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DE LAMAR LECTURES
1926-1927

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH

DE LAMAR LECTURES
1926-1927

BY

F. NEUFELD, ALFRED E. COHN, GEORGE H. F. NUTTALL, EDWARD FRANCIS, WILLIAM H. PARK, ALPHONSE R. DOCHEZ, VERANUS A. MOORE, EDGAR L. COLLIS, EARLE B. PHELPS, MARSHALL A. BARBER

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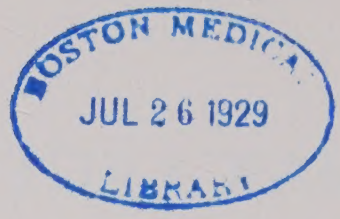

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DE LAMAR LECTURES

A series of popular lectures in personal and public hygiene is arranged each session, by the School of Hygiene and Public Health of The Johns Hopkins University.

The object of these lectures is to bring before the public the general facts and points of view of modern hygiene, with the hope that in this way the School may serve as a center for the distribution of useful knowledge in all matters pertaining to sanitation and preventive medicine.

These lectures are supported from the fund bequeathed to the Medical School by Joseph R. De Lamar, in accordance with the wish expressed in his will "to give to the people of the United States generally the benefits of increased knowledge concerning the prevention of sickness and disease and also concerning the conservation of health by proper food and diet."

This volume includes the lectures given in the sixth series, during the session of 1926–1927, at the School of Hygiene and Public Health.

CONTENTS

1. Natural immunity in its significance for epidemiology. By F. Neufeld, M.D., Director, Robert Koch Institute for Infectious Diseases, Berlin, Germany.... 1

2. The variability of bacteria with especial reference to infectious diseases. By F. Neufeld, M.D., Director, Robert Koch Institute for Infectious Diseases, Berlin, Germany..... 13

3. Heart disease from the point of view of the public health. By Alfred E. Cohn, M.D., Member of the Rockefeller Institute for Medical Research, New York City..... 24

4. Some pioneers in parasitology. By George H. F. Nuttall, M.D., Quick Professor of Biology, Cambridge University, Cambridge, England..... 78

5. Tularaemia. By Edward Francis, M.D., Surgeon, United States Public Health Service, Washington, District of Columbia..... 94

6. Etiology, prevention, and serum treatment of measles. By William H. Park, M.D., Director, Bureau of Laboratories, New York City Department of Health, New York City..... 116

7. The preparation and use of scarlatinal streptococcus antitoxin. By Alphonse R. Dochez, M.D., Professor of Medicine, Columbia University, New York City..... 141

8. Bovine tuberculosis in its relation to man. By Veranus A. Moore, Ph.D., Dean New York State Veterinary College, Cornell University, Ithaca..... 159

9. The personal factor in coal-mining. By Edgar L. Collis, M.D., Professor Preventive Medicine, Welsh National School of Medicine, Cardiff, Wales... 178

10. The environment in relation to health. By Earle B. Phelps, Professor of Sanitary Science, Columbia University, New York City..... 192

11. Some criteria of the results of malaria control measures. By Marshall A. Barber, M.D., Special Expert, United States Public Health Service, Washington, District of Columbia..... 210

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NATURAL IMMUNITY IN ITS SIGNIFICANCE FOR EPIDEMIOLOGY[1]

PROFESSOR F. NEUFELD

Director, Robert Koch Institute for Infectious Diseases, Berlin

Generally speaking, the course of an epidemic outbreak, as well as that of a single case of infection, is ruled by four factors, two of which depend upon the microbe and the two others upon the host. The first two factors are the number and the virulence of the micro-organisms; the others, the natural and the acquired immunity of the host.

Natural immunity is the sum of constitutional resisting powers which the individual has inherited from his parents, liable, however, to be essentially influenced by environmental factors, such as nutrition, climate, etc. Acquired immunity may be defined as being caused exclusively by those means of defense which the organism itself has elaborated under the stimulus of microörganisms or their products. Hence these powers are directed specifically against certain definite agents.

It is, however, not always easy to differentiate both these forms; besides, the terminology used by different authors varies somewhat. As is well-known, a suckling is much more resistant to many infections than are his brothers or sisters one or two years older; for this immunity he is indebted to his mother who, after a previous infection with measles, diphtheria, etc., possesses protective substances against these diseases in her blood, as well as in her milk. If the suckling becomes immunized through the milk, there is no doubt one should speak of the immunity as acquired, but it likewise seems reasonable to use the same term for the antibodies inherited with his mother's blood, though it is not the suckling but the mother who has acquired them. In this connection, therefore, I think it better not to use the term "inherited immunity," since most inherited resisting powers are of quite a different order.

[1] October 21, 1926.

Natural, or constitutional immunity is perhaps the most important of all factors concerned in the spread of infectious diseases. Nevertheless, bacteriologists for many years have ignored it, and in most of their experiments have been anxious to eliminate this factor as one that might disturb the regular course of their investigations. Thus, bacteriological tests, employing the subcutaneous, peritoneal, or intravenous route for injection, afford rather regular results and will, of course, always be indispensable for studying the properties of bacteria, but do not yield data at all analogous to that occurring during the natural course of an infection. Of course, Koch and many others have infected animals by feeding and sometimes by inhalation, but then nearly always by administering enormous doses, such as never are met with in nature.

Only during the last years has the infection of animals through the natural portals of entry been carefully and systematically studied with graduated doses of bacteria. Typhoid bacilli, organisms of the Pasteurella group, swine erysipelas, streptococci, pneumococci, and anthrax bacilli, all of which, when administered subcutaneously in small doses, killed the animals, were administered to mice, and in the case of tubercle bacilli to guinea pigs (1), have been administered through the skin and the mucous membranes of both the digestive and respiratory tract, by way of the mouth, pharynx, intestines, nose, and conjunctiva, as well as through the lungs. The results of these experiments were very irregular. Just as in the case of spontaneous epidemics, where many individuals escape the exposure entirely, some of the experimental animals were infected and recovered, others showed a chronic form of the disease, or became carriers of bacteria, while only a few died acutely, as is the rule when they are injected subcutaneously with the same bacteria.

As was expected, the skin proved to be the best protected against invading microörganisms. However, just as the spirochetes of relapsing fever and of syphilis are known to penetrate the normal skin, the same proved true for the spores and bacilli of anthrax and for swine erysipelas; while most other septicemic bacteria were able to infect in this way only exceptionally and when rubbed into the skin in very large quantities.

When administered *per os*, anthrax bacilli never proved effective,

and anthrax spores only exceptionally so, whereas mouse typhoid proved most virulent by this route. Thus, the resisting powers of the host are specific to some degree, varying according to the species of bacteria. It becomes evident, therefore, that the difficulties and the irregularities observed in all feeding experiments cannot be explained by the assumption that the issue is chiefly a matter of chance, most of the bacteria being eliminated without coming sufficiently into contact with any part of the intestines, where there is a possibility of their penetrating. If this were true, then in multiplying the doses of the microörganisms, the chance should be multiplied in about the same degree, but quite the contrary is to be observed. For example, in one of Lange's experiments, of a number of mice fed with quite a small quantity of mouse typhoid bacteria, 17 per cent died. A dose a thousand times larger killed only 33 per cent, that is twice as many, and a dose again a hundred times larger killed only 50 per cent of the animals. These facts tend to prove that the irregular effect observed in all feeding experiments is due chiefly to the differences in the natural immunity of the animals exposed, and not to mere chance.

This view is confirmed by further experiments with inhalation and tracheal infection, in which the animals had little more opportunity to dispatch the invading bacteria than following subcutaneous injection. However, even here we see the same irregularities, though of all the natural routes by which microörganisms may enter, the lungs are by far the most susceptible, these organs being least exposed to bacterial invasion under natural conditions, and therefore not like the skin and the mucous membranes of the digestive tract, which are forced to rely chiefly on their own powers of defense. But even by this route, only a few species of bacteria prove able to infect the animals as they do when injected subcutaneously;—mouse typhoid and Pasteurella bacilli in mice and tubercle bacilli in guinea pigs—other bacteria, as for instance pneumo- and streptococci, though of highest virulence when injected subcutaneously, failed in most cases to infect through the lungs.

Thus, we see strong, and to some extent specific defensive powers at work in all cases where microörganisms penetrate through any natural portal of entry. Recent experiments on mice by Webster (2) tend to show that a great part of these powers is transmitted by

inheritance from parents to the offspring. Through several generations Webster mated those male and female mice that had proved most resistant against mouse typhoid, and he succeeded in obtaining offspring many times more resistant against mouse typhoid and at the same time against the toxic effect of bichloride of mercury. From this Webster concludes that the resistance of mice contains important hereditary factors of specific and non-specific kind, and that this resistance may be enhanced in a given population by selective breeding.

Another example of hereditary immunity has been set forth by Hirszfeld (3). He found that normal antitoxins present in the serum of many men (as well as animals), regardless of whether or not they ever came into contact with these bacteria, are transmitted from the parents to their children after the law of Gregor Mendel. Thus these normal diphtheria antitoxins behave quite otherwise than the acquired ones in the case of the suckling mentioned in the earlier paragraphs. These latter, as acquired, not innate properties, are not transmitted by inheritance, but only by passive immunization through the maternal blood. Thus, as in all instances of passive immunity, they are excreted again after some months and, as in the case in real germinal heredity, never prove to be transmitted from the father's side or through more than one generation.

The enhancing of the natural resistance of a given population by selection appears to play an important part wherever infectious diseases are widespread through numerous generations, as small pox and measles, for instance, have been for centuries in nearly all civilized countries. Therefore, when these diseases are introduced into a new country where they are not yet known, the population is affected very seriously. This holds true as well for tuberculosis. I think Behring and Roemer were incorrect in assuming that the high susceptibility of primitive races is caused principally by want of a specific immunity, such as is acquired by infection in childhood by most of us. This explanation could only be accepted if, for example, tuberculosis belonged to that group of diseases to which children are more resistant than adults; in fact, the reverse is known to be the case.

In former times one was accustomed to speak of racial immunity as a proved fact; the high resistance which negroes manifest to

malaria in contrast to that of white people was cited as an example of such immunity. But then Koch discovered that in many tropical countries nearly all children were infected and often died with malaria; so that the immunity of the surviving population is now considered for the most part to be an acquired one. Nevertheless, these facts may be accounted for, in part at least, on the basis of selection.

However, it is likely that besides both these factors there may be a true racial immunity, as was recently shown experimentally by Webster and Pritchett (4) in the case of mouse typhoid, where they found rather great racial differences. Large numbers of inbred mice from different races were used and found to differ consistently in their resistance to the specific infection.

Pritchett (5) established that the natural susceptibility of pure bred mice was influenced, though only to a slight degree, by season. Such influences appear to be of no small importance in the case of many diseases prevailing in our countries. It is well-known that the morbidity and mortality by tuberculosis, pneumonia, catarrhs, meningitis, and other infections show rather regular seasonal curves. In the case of malaria these influences are even more distinct. At present it is usually acknowledged that many malarial infections as acquired in summer or autumn may rest in a state of complete latency throughout the whole winter and only in spring give rise to a sudden attack which often is mistaken for a recent infection. It should be added that some investigators explain this seasonal prevalence as caused by a direct action of climatic factors (and among these especially sunlight) on the evolution of the parasites, and not on the susceptibility of the host.

Also in the epidemic of typhoid fever a seasonal influence is common, manifesting itself in the well-known summer peak. The real causes of this phenomenon are not yet sufficiently cleared up, but some evidence tends to show that in our country at least most of the infections in summer are due to contact with carriers, who perhaps at that time suffer a reduction in the amount of their immunity, accompanied by a disturbance of the equilibrium between microörganism and host and an excretion of greater quantities of the bacilli.

It has long been known that children are much more susceptible to many infectious diseases, such as tuberculosis, meningitis, polio-

myelitis, and diphtheria, and on the contrary more resistant to others—as, for instance, typhoid fever and especially typhus (exanthematic fever). In Poland where this disease is endemic, it is reported to have a mortality rate for children of less than 1 per cent (6). I have expressed the hypothesis (7) that in such cases the high resistance of children might be explained by their faculty of elaborating antibodies more quickly and in larger quantities than adults, but that in contrast to this the normal defensive powers, such as reside in the mucous membranes and the lymphatic system, are weaker than in adults. At least for the last assumption there is at hand some experimental evidence. Very young mice, for instance, prove much more susceptible than adult mice not when injected parenterally, but when fed with nagana trypanosomes (7), or with the smallest quantities of mouse typhoid bacilli which kill them almost invariably; whereas the same doses are effective in full-grown mice only exceptionally. The same difference is even more marked in guinea pigs. Here the full-grown animals are almost absolutely resistant against feeding with mouse typhoid bacilli, whereas quite young guinea pigs may be infected when fed with rather small doses (8).

Webster and Pritchett (9) have given experimental evidence for the influence of diet on the resistance to mouse typhoid. They fed mice on a special diet described by McCollum, and found them to be much more resistant than their fellows fed in the usual way, the mortality rate of the latter being five times greater.

The well-known fact that want of vitamins favors many infections has recently been confirmed by experiments on animals which showed that it is not the inhibition of the production of antibodies, but the lowering of the natural resisting powers that makes animals more susceptible (10, 11).

This has been proved, for instance, in rats, doves, and rabbits which were suffering from want of vitamin A or B and injected parenterally with different species of bacteria, such as anthrax or pneumococci (11, 12). However, in these experiments, the animals were already in a very poor condition and their temperature was far below normal at the time when the infection took place. Further experiments showed that an administration of anti-febrile drugs had a similar effect, so it is not evident how far there was a specific effect of the want of vitamins.

The observations of Bieling (13) and Heymann (14) are perhaps of greater interest since the guinea pigs used in their work were in a state of mild and chronic scurvy. Such animals proved distinctly less resistant to tuberculous infection. Bieling lays stress on the point that these animals, dying much earlier than the normal controls infected with tubercle bacilli or those subjected merely to the scurvy diet, showed no evidence of either severe scurvy nor of tuberculous infection sufficiently extensive to explain the deaths. It is not impossible, therefore, that in these experiments spontaneous secondary infections may have played some part.

Many authors working in this field agree that guinea pigs suffering from scurvy are highly susceptible to spontaneous infections of various kinds. This was also observed in a series of experiments recently carried out in our institute. We wished to determine whether such animals were liable to an infection with pneumococci and Pasteurella by feeding or inhalation. Both of these organisms when administered in this way to healthy animals rarely prove infective. The scorbutic guinea pigs died sooner or later after the infection, as described, but, besides these, nearly all of the uninfected scorbutic controls died as well and were found to harbor the specific organisms. Pasteurella bacilli were found most commonly but some, including a number which were experimentally infected, showed a mixed infection with both species (15). Hence, there can be no doubt that in these cases bacteria present on the mucous membranes of healthy animals were enabled to penetrate through the natural means of entrance and to kill the animals, because their natural immunity had broken down from lack of vitamin.

Both pneumococci and Pasteurella bacilli are known to us as common incitants of epidemics among the guinea pigs in our stables, and there can be no doubt that the essential cause for the outbreak of epidemics of this kind is not the mere presence of the microörganisms, but the lowering of the natural resistance of the animals by any special injury. Thus, under natural conditions, as well as in the experiment just described, this injury to natural resistance may be the want of vitamin. This possibility was first considered by Theobald Smith (16) who observed in his laboratory an epidemic which he ascribed to insufficient food, especially to the want of fresh vegetables.

But there are other conditions which may lead to the same results. An epidemic which killed more than 200 of our guinea pigs in two months was found to be caused by exposure to cold (17, 18). From this epidemic, Pasteurella bacilli and pneumococci were cultivated repeatedly and subsequently given to healthy animals; they proved to be highly infective when given subcutaneously, even in the smallest doses. On the contrary, when given in doses at all comparable with those occurring in nature, they did not infect by feeding or inhalation.

In this connection, I wish to recall the experiments carried out long ago by Pasteur, by Lode and by Ronzoni (19), who exposed fowls and guinea pigs to cold—though indeed by somewhat crude means—and found them susceptible to an injection of anthrax and other bacteria not effective in healthy animals.

It appears that among our domestic animals infections by microorganisms which are unable to attack normal animals are of considerable significance. In these cases an epidemic outbreak can only be explained by environmental influences which render the animals in some way less resistant. Such may be true in many outbreaks of swine erysipelas, fowl plague and chicken cholera. As to the fowl plague, Doerr (20) has recently related new researches about the mode of infection. He found the filterable virus to be infective parenterally in very small doses, whereas feeding even with enormous quantities was rarely effective. From this he concluded that the disease is not likely to be transmitted in this way under natural conditions. I, myself, would not concur with this opinion, but would merely state that the infective agent is not able to attack normal animals in this way, and that it needs some special condition interfering with the natural immunity of the animals to make an epidemic outbreak possible. This view, I believe, is supported by numerous reports of veterinarians on epidemics of this, as well as other diseases—swine erysipelas, chicken cholera and Pasteurella infections—among other animal species. Most of these microörganisms are unable to infect regularly healthy animals by natural ways, except in very large doses.

The same holds true for many infections prevalent in man. Long before experimental evidence was available, the enormous influence of nutrition on the diseases of children had been emphasized by

prominent physicians and above all by Czerny. As for scurvy, I call attention to a recent report by Abels (21), who is of the opinion that the chief danger of scurvy and as well of "pre-scurvy" is that it favors infections by common microörganisms which exist as harmless saprophytes on the skin and the mucous membranes of many healthy persons.

Also the influence of cold is known more from the daily experience of practitioners than from experiment. Cold as well acts chiefly by lowering the resistance against saprophytic cocci present in the nose, mouth and pharynx. In a previous report (22) I have pointed out, and I would like to cite it here, that it seemed advisable to me to put the question how far unhealthy and unnatural conditions of life may favor or make at all possible the invasion of these organisms. I suggested that we might start from the hypothesis that nature has not given us these microörganisms as enemies to live continuously in our body, but that special conditions are necessary before they become enemies. There is some evidence that among many unnatural habits connected with our state of civilization, want of fresh air, want of reasonable hardening, too thick clothing and above all, perhaps, the overheating of the rooms as usual in our northern countries may be the principal injuries favoring the so-called colds—and perhaps small children are most affected by these injuries.

In some cases traumatic or chemical irritation may give rise to an infection by microörganisms otherwise living as harmless saprophytes on the mucous membranes. According to a recent report by Seligmann (23), this may indeed happen, and perhaps not exceptionally, in the case of sporadic meningitis, where a simple blow on the head or contusion activates a latent meningococcic infection.

The fact that syphilitic infections of the central nervous system, especially paralysis, become more and more prevalent may perhaps partly, not exclusively of course, be explained by over-exertion of the nervous system. I should not venture this assumption if we had not a certain analogy for it. In our institute, as well as in others, where persons bitten by rabies-suspected dogs are treated after the method of Pasteur or some modification of his method, we are sorry to observe from time to time cases of paraplegia, sometimes milder,

sometimes more severe, and sometimes ending fatally—cases which there is no doubt are due to the injection of the fixed virus, as modified by many passages through rabbits and in this state proving inoffensive in thousands of patients, even when injected daily for three weeks, as it is used in most of the institutes. Such unfortunate occurrences prevail among mental workers (24, 25, 26, 27).

From the Pasteur Institute in Java (28) there has recently appeared a careful report relating to several thousands of patients subjected to the same Pasteur treatment. Most of them were natives—only a few Europeans—but the cases of paraplegia were observed almost exclusively among the Europeans. The differences in susceptibility present here are the same as those of syphilitic affections of the central nervous system; hence the same predisposing conditions may be at least partly responsible in both cases.

Lastly, I wish to mention that very often one infection may activate another latent one by reducing the natural immunity. Perhaps all infections may act more or less in this way, but there are some in which this fact is so apparent that we are justified in observing therein the chief effect of those incitants. This is the case, for example, in measles and in influenza, the fatal issue being caused nearly always by secondary infections.

In some European countries there have recently been observed cases of lethargic encephalitis in children soon after vaccination. The most likely explanation, as given by Levaditi (29) and others is that a latent infection with encephalitis virus, which may or may not be identical with the herpes virus, has been activated by the vaccinal eruption.

It is well-known how difficult it may be to ascertain the presence or absence of certain bacteria in healthy animals. As I have just related, our guinea pigs, set on scurvy diet, nearly always died with a Pasteurella infection, and so did many rabbits in an epidemic I have already spoken of, which proved to be caused by exposure to cold. These bacteria, therefore, must have been present in nearly every healthy animal, and yet we were unable to recover them from most of them. Lange (17) tried to make some rabbits, in the pharynx of which he had searched in vain for Pasteurella bacilli, susceptible to a natural infection by cauterizing the nasal mucosa with silver nitrate.

The effect was a surprising one. Three of eight animals treated in this way died in three or four days with a Pasteurella infection, and of the five others, two showed on the mucous membranes the same bacilli. The three remaining animals were cauterized another time, whereupon two of them presented the Pasteurella bacilli and came down with rather heavy catarrh. Thus, nearly all of those animals must have had, from the beginning, the bacteria somewhere on their mucous membranes, in spite of the fact that we were not able to find them by culture.

Thus we have seen how many different conditions are at work to break the natural immunity of the host, and to activate latent infections. I think we are justified in citing among those infections anthrax, prevailing until now in many countries among cattle and sheep. Since Koch's discoveries many investigators have tried to infect animals of different species, all of which are highly susceptible to a parenteral injection, by natural ways, and except when administering enormous doses, such as are never met with in nature, have nearly always failed. So we must assume that normal animals are highly resistant to anthrax, and that this resistance must be reduced by some special condition not yet known before an epidemic may break out. This is the more likely, since it has been reported recently that in some parts of Asia Minor, nearly all goats are carriers of spores of anthrax which seem to grow luxuriantly on the hair (30, 31, 32).

Thus, even in the case of infections such as anthrax, which seemed to us to be the best known of all, many questions must remain undecided. In the wide field of epidemiology, there is yet much work to be done with the coöperation of the bacteriologist, the pathologist, the clinician, and the veterinarian. Perhaps, however, we may hope that the main progress will come from the type of experimental work that has been started so brilliantly in this country.

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VARIABILITY OF BACTERIA[1]

PROFESSOR F. NEUFELD

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About fifty years have elapsed since Robert Koch (1) published his researches on the etiology of wound infection. In closing his paper, he gives as the most important result of his investigations the evidence that there are different species of pathogenic bacteria, but that each itself is invariable. Koch says, "A special form of bacteria is associated with every disease, and this form remains unaltered, no matter how many times the disease is transferred from one animal to another."

One year before, the famous botanist Naegeli (2), in his treatise on "The lower germs and their relations to infectious diseases," had taken exactly the opposite point of view, asserting that he had for ten years examined thousands of different forms of bacteria without finding any reason to separate them into specific forms. Contagious microörganisms, he asserted, change into putrefying forms, and *vice versa;* and to the sober physiological mind, the theory of germs as specific agents of diseases appeared almost fantastically naïve, reminding one of the personifications by which primitive peoples sought to explain great natural events.

These opposing views clearly show the real significance and the importance of the doctrine of the specificity of infectious microorganisms, a theory which may be said to represent the quintessence of Koch's life work. This doctrine has brought order into the chaos of microörganisms imputed as causing diseases; it is the basis of all our diagnosis, prophylaxis, and the specific therapy of infectious diseases.

It easily happens that doctrines of such fundamental and comprehensive importance are, in the course of time, taken in a too rigid and dogmatic sense, and are generalized to an unwarranted extent. Koch's doctrine has, I believe, escaped this fate no more than have the doctrines of Darwin or Gregor Mendel.

[1] October 22, 1926.

For some time, however, opposing views have been promulgated by an increasing number of bacteriologists, and the variability of infectious microörganisms, a phenomenon placed beyond doubt since the great discoveries of Jenner and Pasteur, has once more become the object of general interest. A thorough study is being made of the changes which bacteria undergo, not only the changes which we are able to produce *in vitro*, but also those occurring in the natural course of an infection. These latter phenomena, namely, the changes in bacteria which take place while in the body of the host and under its influence, are, in my opinion, of special practical interest for the clinician as well as for the epidemiologist. They have of late been the object of my own and my collaborators' researches, and they will form the chief topic of the present lecture.

As you are doubtless aware, for many years and up to the present time, the relations existing between the diphtheria bacilli and the so-called diphtheroids have been much discussed. The latter are frequently found in the form of Xerose, Hoffmann, and other types, on the mucous membranes and the skin of healthy persons and animals. The question arises: Are these microörganisms related to the true Loeffler bacilli, and do they develop from them; or, are they to be regarded as belonging to entirely different species, the representatives of which are at times indistinguishable?

Bernhard and Paneth (3), working in my laboratory nearly fifteen years ago, endeavored to solve the problem experimentally. They injected diphtheria bacilli intravenously into guinea-pigs and rabbits, and on killing the animals a day or two afterwards, succeeded in recovering from their organs non-toxic diphtheroid bacilli. They observed the same transformation *in vitro* when they inoculated diphtheria bacilli into undiluted serum of human beings or guinea pigs.

Some workers, however, have objected that the original strain of bacilli used in these experiments might have contained from the beginning a mixture of diphtheria and diphtheroid bacilli. Therefore, Levinthal (4) recently attacked the problem by means of the single cell method. Starting from a single cell of a highly toxic culture, he succeeded in splitting off a number of modified strains which proved absolutely atoxic and which morphologically and in their cultural and staining properties, behaved partly like Xerose, partly like

Hoffmann bacilli. The same variants were regularly cultivated by him from the blood and organs of guinea pigs killed by intravenous or subcutaneous injections of the same virulent diphtheria strain. Crowell (5), in this country, has obtained similar results.

We may assume that a like transformation of diphtheria bacilli into atoxic diphtheroids regularly takes place in human beings, and that the final issue of the diphtherial infection depends not only upon the antitoxic content of the blood, but also upon the transforming power of the individual. Patients who are not able to transform the virulent into atoxic bacilli may partly on this account succumb to the infection. The cases of diphtheria in which typical toxic bacilli appeared in the urine nearly always ended fatally, whereas the urine of patients afterwards recovering from the disease often contains atoxic diphtheroids which we may presume to be modified diphtheria bacilli (6).

Recently, Killian (7, 8) succeeded in imitating more closely the process of human infection. He brought diphtheria bacilli into the mouths of guinea pigs and mice, and was able to cultivate atoxic diphtheroids some hours later from the cervical glands of the animals.

We may assume that the bacilli undergo the same degeneration, not only when passing through the mucous membranes, but also when growing on their surfaces. In this way, most of the toxic bacilli present on the tonsils at the height of the disease may be disposed of. As is well-known, diphtheroids are frequently found in convalescents, but of course the objection that they might have been present before cannot be directly refuted.

In some cases atoxic diphtheria-like bacilli have been found as incitants in cases of chronic, obstinate bronchitis (9), and we may assume that these also are derived from virulent diphtheria bacilli.

Similar changes have been observed in highly virulent streptococci and pneumococci passing through mucous membranes. These microörganisms, in contrast to the diphtheria bacilli, are able to grow and multiply in all organs; nevertheless, they are seriously injured by simple passage through a mucous membrane. From the cervical and mesenteric glands of mice and guinea pigs fed with these cocci, weakly virulent or avirulent variants could be cultivated, which showed at the same time morphological and cultural changes

(7). The cocci in these experiments soon disappeared from the surface of the mucous membranes, and here also there seemed to develop avirulent and otherwise altered forms; but as many similar cocci are to be found in the normal pharynx, it is not possible to study here the degenerative changes.

Thus we may ascribe to the mucous membrane itself highly active defensive powers. Presumably we may explain in this way the peculiar fact that the urinary bladder and also the gall bladder, though communicating directly with other mucous membranes rich in bacilli, themselves remain sterile.

The lungs also are endowed with the power of destroying many species of bacteria, such as, for example, highly virulent streptococci and more especially pneumococci. For this reason, mice which are allowed to inhale rather large quantities of the cocci, only rarely become infected; and if the animals are sacrificed at various times after inhalation and cultures are made from their lungs, one is able to observe the rapid disappearance of the bacteria (10, 11).

Similarly, from the cervical and mesenteric glands of mice fed with spores of anthrax and of rats fed with typhoid bacilli, variants of lowered virulence and altered rate of growth have been cultivated (12).

It has long been known, especially from the investigations of the Royal Commission on Tuberculosis, that tubercle bacilli cultivated from cases of lupus and verrucous tuberculosis of the skin often proved to be only slightly virulent. In some cases even guinea pigs are not severely infected by such material, so that some times they may recover completely. From other organs also, chiefly from the glands, modified and weakened strains of tubercle bacilli have been recovered (13, 14, 15). If it were not so difficult to cultivate such strains, perhaps they would be met with rather frequently. There is strong evidence for the assumption that a sort of degeneration often takes place when tubercle bacilli in small quantities, such as commonly obtain under natural conditions, pass through the mucous membranes of the pharynx, the intestines, the nose or the conjunctiva. Probably this accounts for the fact that under such conditions most of the guinea pigs escape infection, except those in which the disease takes a mild and more chronic course. When the animals are in-

fected subcutaneously or by inhalation with virulent tubercle bacilli (16, 17), no such sequence of events occurs. We may assume that human beings behave in a similar manner.

Even when mice are infected subcutaneously with the most virulent streptococci, degenerative changes have been observed. If such mice are killed some hours after inoculation and cultures made from their organs on blood plates, sometimes one is able to observe among hundreds of typical colonies of *Streptococcus hemolyticus* a single colony, or a few colonies of *Streptococcus viridans* (18). Such colonies generally prove to contain weakly virulent cocci, which, however, often regain rather quickly their virulence and their power of hemolysis.

Even more labile variants may, presumably, often escape observation, because they have lost the property of permanent growth on our nutrient media. All the investigators who have searched for such variants have been impressed with the difficulty of cultivating the modified strains, or at least of cultivating them for any considerable period of time. This holds true for diphtheria bacilli, as well as for streptococci and pneumococci. When the degeneration has proceeded far, it has been found that such bacteria, in our experiments at least, could never be cultivated for many generations (7).

In the case of the *Streptococcus viridans* derived from patients with endocarditis lenta, Schottmüller has already reported that only exceptionally can they be cultivated for a long period of time. Obviously the cocci have been transformed while under the influence of the human body and its defensive powers.

That such non-viable forms may occur rather frequently has been suggested by many recent observers. Mice infected *per os* with small doses of mouse typhoid bacilli, or exposed to a slight, natural infection in their cages, very often succumb to a chronic infection, without it being possible to cultivate the bacilli from their organs. Similarly, when mice were fed with streptococci and became chronically infected, it has proved difficult to recover the cocci from their tissues. This peculiar fact, I believe, is only to be explained by some degenerative change of the bacilli.

Presumably during the struggle taking place between the inciting agent and the host, the bacteria have a tendency to produce variants

which, though yet living, can grow only with difficulty in the animal body, as well as on our nutrient mèdia. These conditions seem to be closely related to the Twort-d'Herelle phenomenon. Many observers have pointed out that the lytic substance of d'Herelle is not only an agent which destroys bacteria, but also a means of producing bacterial variation, and I am in agreement with Eastwood (19) who asserts that in all processes of bacterial variation, even where, as far as we can see, no bacteriophage is coöperating, there frequently appear variants which prove non-viable. Eastwood further states: "There is usually an intermediate stage before the variants disappear entirely; some of them are just viable, though tending to subdivide into non-viable forms."

In this connection I wish to quote an observation made by Morgenroth (20) on nagana infected mice which he treated with tantal. He found that this element does not act at all as a trypanocide, but modifies the trypanosomes in such a manner that they may be further propagated for a very few passages in mice; later, they die.

These phenomena seem to me in some way analogous to the well-known observations made on the higher plants and animals, where one sees frequently, particularly if different species or races rather remote from each other are crossed, the appearance of individuals that prove sterile, or at least are not capable of propagation when mated among themselves. In other cases, the variants themselves prove to be non-viable, and one then speaks of the "lethal factor."

In the course of such variation processes, bacteria may produce minute filter-passing modifications. As is well-known, filterable variants of typhoid, paratyphoid, dysentery, and tubercle bacilli have been described of late by several investigators; and as far as the bacteria of the typhoid group are concerned, the variation has been ascribed to the bacteriophage. I do not wish to enter into the details of these observations, inasmuch as I have personally no experience in the matter, except that I witnessed the investigations of Levinthal (21) on pneumosintes cultures, which he was able to change at will from filterable to large forms resembling the Pfeiffer bacillus and *vice versa*, according to the nutrient medium.

There can be no doubt that pathogenic bacteria undergo manifold changes from the moment they invade a host. However, they do

not merely degenerate, but often acquire new properties useful to them, especially the faculty of growing luxuriantly on the normal mucous membrane. In this connection I wish to cite a recent observation made by Webster (22). Webster, in the course of his studies on snuffles in rabbits, recovered several strains of the infectious agent (*Bact. lepisepticum*) of differing pathogenicity. When he administered them intranasally to rabbits, it appeared that highly virulent strains were not capable of vegetating in the nasal passages of the animals, while strains of lower virulence survived and multiplied for long periods. Even the variants arising from the virulent bacilli, when brought into the nose, persisted for only a few days.

The bacilli may profit in still another way in their transformation into less virulent variants, namely, by their loss of antigenic properties (8). They no longer stimulate the production of antibodies, which process forms the most powerful means of defense possessed by the infected host. Hence the appearance of weakly virulent variants may ultimately prove dangerous to the host. This is probably the reason why the final prognosis in endocarditis lenta is less favorable than in the severest cases of acute streptococcal infection.

The same condition holds true for an experiment on mice recently observed in Manteufel's laboratory (23). The mice were infected with a strain of relapsing fever, partly by rubbing the material into the skin and partly by peritoneal injection. The latter animals fell ill promptly, and numerous spirochetes were found in the blood at an early stage; whereas in the case of infection through the skin, the incubation period was distinctly longer, the blood infection weaker, and the whole course of the disease protracted. Finally, however, the cutaneously inoculated mice showed about double the mortality rate of those infected peritoneally.

As you are doubtless aware, certain investigators have formulated the hypothesis that a somewhat similar effect may be produced in the treatment of syphilis with salvarsan (and perhaps also with mercury), namely, that by checking the development of the spirochetes at the onset of the infection, we may inhibit at the same time the formation of antibodies, with the result that the few remaining spirochetes, changed perhaps into weakly virulent forms under the influence of salvarsan, may tend to cause chronic systemic infec-

tions, especially paralysis. This hypothesis is far from being proved, but I think we cannot deny the possibility that it plays some part in the intricate problem of a threatening prevalence of paralysis as observed in many countries. Indeed, it has been proved experimentally that pathogenic microörganisms, when treated with chemotherapeutic agents, often change into modified forms which are less virulent, but at the same time less susceptible to both antibodies and chemical agents (24).

In some cases, though rather exceptionally, pathogenic microbes may give rise to variants which are more or less stable and capable of inducing a modified form of disease. Thus, from small pox virus there may be derived, under conditions not yet sufficiently known, the rather harmless modification designated as "alastrim," which it seems may occasionally revert into the original virulent virus. On the other hand, we may obtain by means of one or several passages through cattle the virus of cow pox, which has never been observed to revert to the original type.

Here again, the microbes seem to lose not only much of their virulence, but of their viability as well. The cow pox virus apparently is not able to pass for any length of time from cow to cow. Gins (25) believes that even in human beings, the vaccine cannot be cultivated for an unlimited period, but gradually loses its virulence, though only in the course of years.

An analogous change of a virus into a less virulent, but still pathogenic variant, may perhaps occur in typhus, many investigators regarding the so-called Brill's disease, as observed in New York, as due to a mutation form of the incitant of typhus.

Nearly all the variants we have spoken of are what we call minus variants, and the question arises: Have any plus variants been observed? Is there evidence available that microbes may not only lose, but also acquire qualities, especially new pathogenic properties?

Broadly speaking, I think we must answer this question in the affirmative, but at the same time we must add that, as in the case of the higher plants and animals, the appearance of newly acquired properties is observed very seldom and can be demonstrated experimentally only in exceptional cases.

In this connection I may quote only two observations made in my

own laboratory. The first was made many years ago by Kuhn and Woithe (26); it concerns the phenomenon designated later on as "paragglutination." From the feces of chronic dysentery patients many coli bacilli, and in some cases also cocci, growing on the agar plates, were agglutinated by an antidysenteric serum in about the same dilutions as the dysentery bacilli themselves. Later on, many analogous observations were made on typhoid and paratyphoid patients, and even more often in carriers. From the feces, urine, and even the blood of such persons, strains of coli and other bacteria were obtained, which showed the same phenomenon of paragglutination with typhoid, or paratyphoid serum (27). In these cases, a bacillus seems to pick up a specific antigenic substance derived from another microbe of quite another species growing in its neighborhood, and to assimilate the strange material in such a manner as to pass the newly acquired property by inheritance to many following generations—not indeed forever. It seems that in all cases the paragglutinating bacteria sooner or later lose, sometimes only after a year or more, the paragglutinating property. Many bacteriologists believe that the so-called X19 strains of proteus bacteria isolated by Weil and Felix, and others, from cases of typhus, are common proteus bacilli which have gained the property of paragglutination with antibodies originated by the action of the unknown typhus virus. If that were true, and I believe it is likely, then there would be an instance of paragglutination remaining unaltered through many years. Of course, an attempt has been made to imitate this process *in vitro*, and Kuhn and others have succeeded in producing artificially paragglutinating bacteria, not, however, stable in this property (28, 29, 30).

The second observation in this field has been made recently by Levinthal (31), who, starting from a single cell pure strain of Pneumococcus I, made absolutely non-virulent (so that mice were not infected when injected with the sediment of 10 cc. of broth culture), succeeded, as did Felton and Dougherty (32), in converting this strain again to its highest degree of virulence, thus corroborating previous observations made by Schiemann, Griffith, and others. However, these latter observations, in which the single cell method was not employed, were open to the objection that the original strains

had possibly contained a few virulent microörganisms. However, in this case I think we are not justified in saying that the microorganisms have, in the strict sense of the word, acquired a new property, but only that they have regained an old one which may have remained in them potentially in a latent form.

The same holds true for older observations, such as those of Pasteur, who was able to make a weakened modification of anthrax revert to the original virulent form.

Thus, an acquisition of a real new pathogenicity has, in my opinion, not been induced artificially up to the present time, and under natural conditions seems to occur only under exceptional circumstances.

Not long ago, nearly all investigators seemed to agree in the assumption that the epidemic waves, the more or less certain rise and decline of an epidemic, are not only accompanied, but even caused by an increase and a following decrease of virulence of the inciting agents. Some authors, indeed, cautiously left open the question whether there was to be assumed a real modification of the microbes, or a mere process of selection. It is to the work of Webster (33) that we owe the evidence that this conception is erroneous. At least it has been demonstrated by him that the rise and fall of the epidemic waves may be sufficiently explained, not by changes in the virulence, but in the number of the infectious agents available at a given time; and that in two diseases carefully studied, namely, mouse typhoid and Pasteurella infection of rabbits, there is indeed no enhancing of virulence at all. Thus, until further evidence is at hand, we are not justified in speaking of an enhancement of virulence as an essential or even as a common factor in the rise of epidemics.

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HEART DISEASE FROM THE POINT OF VIEW OF THE PUBLIC HEALTH[1,2]

ALFRED E. COHN, M.D.

The subject of heart disease has become a matter of great public interest since it was pointed out a few years ago that the death rate on this account seemed to be rising. It soon became established that a rise has actually taken place. The experience with tuberculosis and with other infectious diseases suggested the idea that assiduous attention to heart disease, like that which had been devoted to these other ailments, might yield similar reductions in morbidity and mortality. Associations for the prevention and relief of heart disease were accordingly formed. It was only later, in more recent years, that certain facts began to be subjected to more searching analysis in order to learn, especially from the point of view of prevention and relief, what actually is the situation in respect to this group of diseases. For it required no great amount of reflection to appreciate the fact that unlike tuberculosis or any other disease of bacterial origin, heart disease or what went by this name, was composed not of a single entity, but of diseases etiologically as distinct as the acute rheumatic affections, syphilis and arterial degeneration. At first it was not clear, and indeed in a general way it is not clear now, either in this or, in point of fact, in other connections that arterial decay and degeneration of the heart might not be diseases, but the expression of the senescent process. To give expression to the underlying facts we shall in the end, perhaps, be obliged to make a distinction between the decrepitude of old age, a normal and natural growth process, and diseases in old age. That this distinction has importance in the problem I am to discuss, considerations, later to be urged, may make apparent.

When the increase in diseases in connection with the circulation became evident it was natural to compare the curve of death rates as the result of chronic diseases with that of the total death rate curve.

[1] November 15, 1926.

[2] From the Hospital of the Rockefeller Institute for Medical Research, New York.

Figure 1 illustrates the result of this comparison in New York City for the years 1868–1921(1). At the beginning of this period the ratio of deaths from chronic diseases to the total death rate was about as 1 is to 15. At the end of this period the ratio was about as 1 is to 2. It appears, therefore, that the chronic diseases have taken on a quite new importance. The reason for this is seen in part in studying during

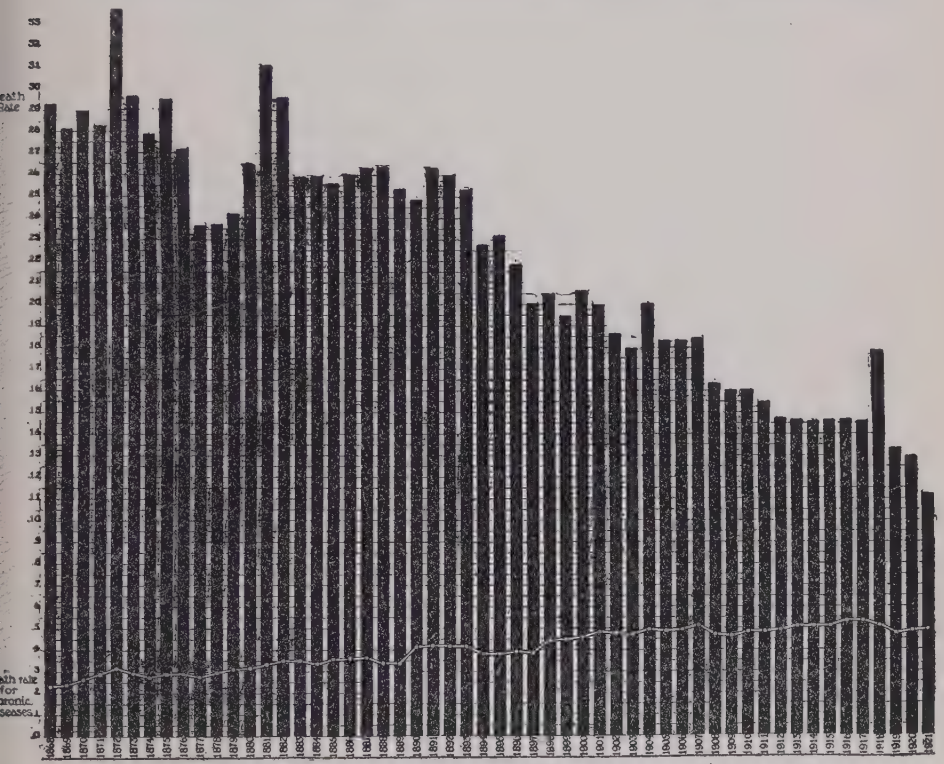


FIG. 1. Chronic diseases include cancer, Bright's disease, nephritis, apoplexy, cirrhosis of liver, diabetes and all circulatory diseases.

the same period of time the changes in death rate which have taken place in certain acute diseases, such as diphtheria, scarlet fever, whooping cough and typhoid fever, as exemplified in New York City. (See fig. 2.)

After 1882 the curves of all of these diseases began to fall, and after 1894, when antitoxin against diphtheria was first used, to fall signifi-

cantly. It is perhaps worth pointing out that the fall occurred even in those diseases against which there was no specific antidote.

That the fall in infectious diseases might influence the death rate movement in heart disease also requires consideration.[3] (See fig. 3.)

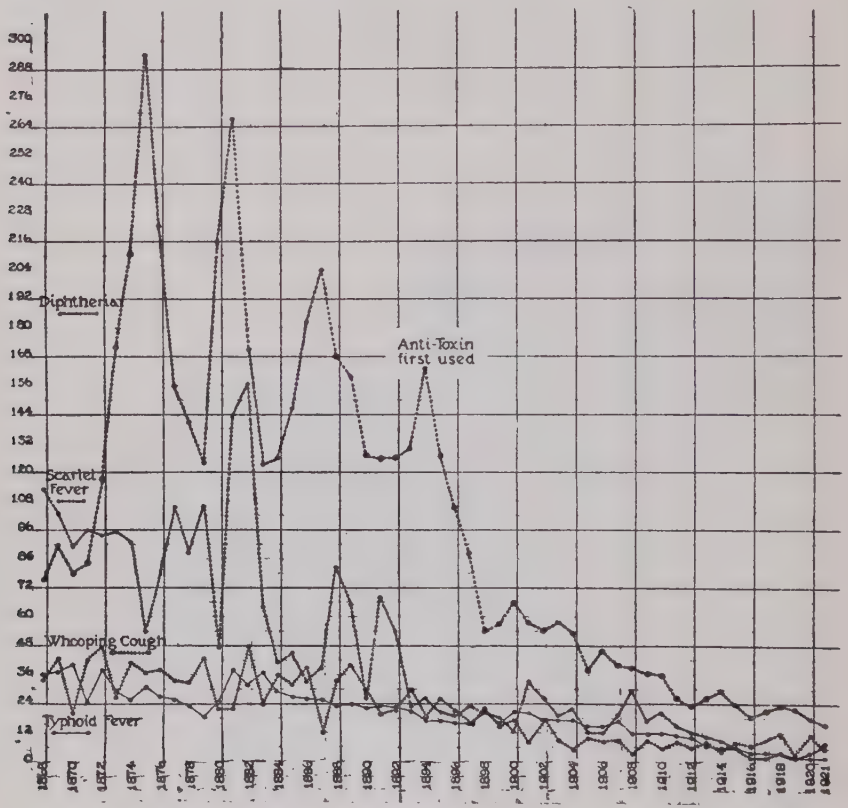


FIG. 2. Decrease in death rate per 100,000 population in New York City for typhoid-diphtheria-whooping cough and scarlet fever during the past 53 years.

That the figures before 1900 are unreliable, due to the many phases of faulty technic employed in collecting them, is notorious. For this reason they probably fail to exhibit the course of events and can do no more than represent an approach to the facts. This

[3] I am much indebted to Miss Alice Whittemore for accumulating the data on which this curve is based, and for arranging these curves, as well as those in figure 4.

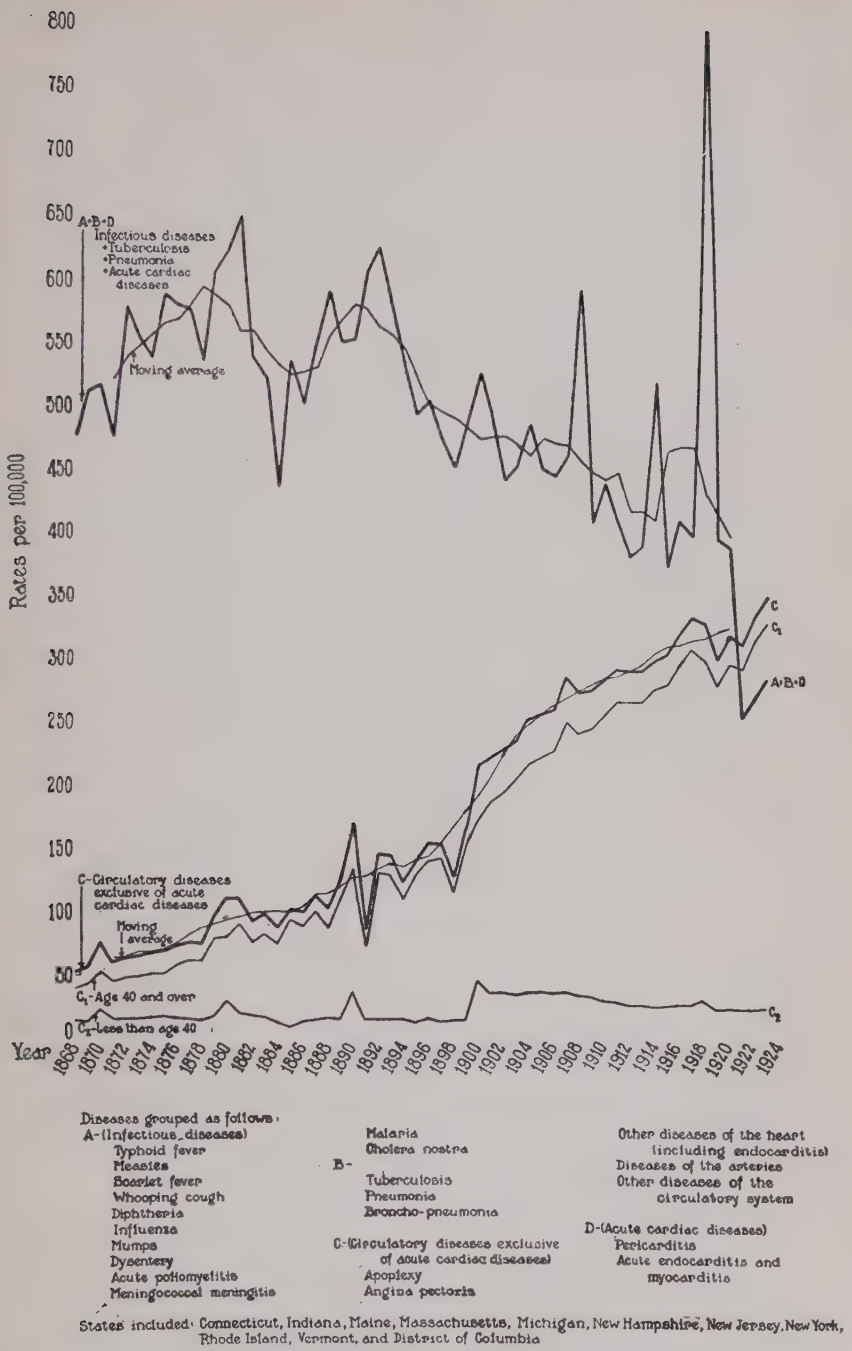


FIG. 3. The peaks in curve C_2 in this figure and in figure 4 are due to data taken from United States Census years. After 1900 all data are taken from the United States Census.

is unfortunate in view of the important inferences which could otherwise have been drawn. It is, however, important to call attention to the inferences which are implied in considering them.

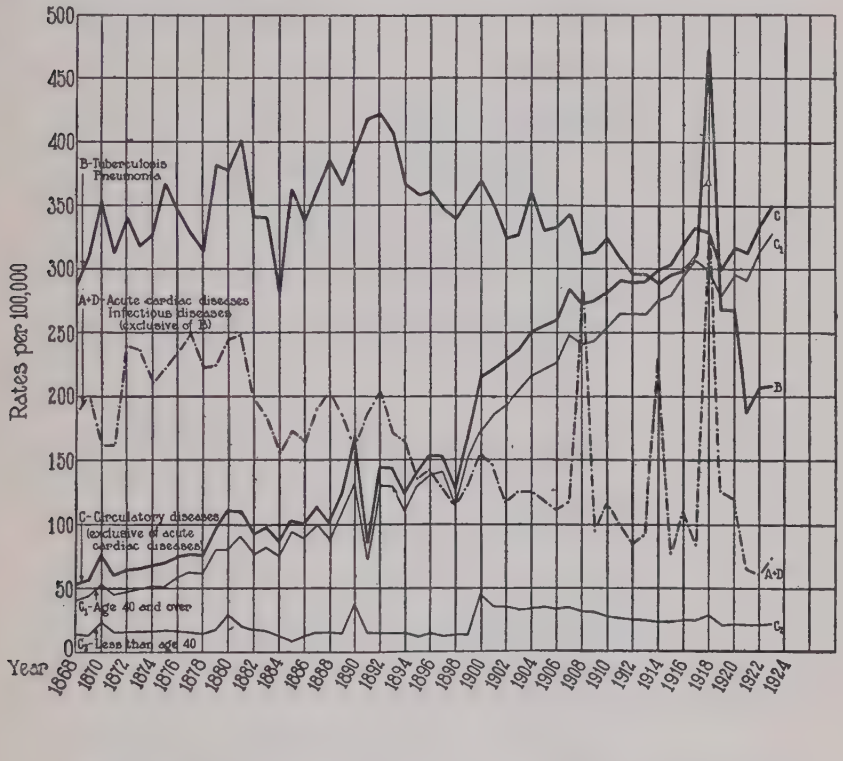
Before 1896, curve *C* of the chronic circulatory diseases, exclusive of acute circulatory disease, rose gradually. For this rise I have as yet no explanation to offer. In the moving average of this curve, in the year 1896, there is a sharp inflection, the section afterward showing an abrupt rise. The foot point of the rise is referable probably to the year 1898 in curve *C*. The high point of the curve *A B D* of infectious diseases is found seventeen years earlier, in the year 1881. I entertain the belief, as do many others, that the fall in infectious diseases is intimately related with the rise in the cardiac death rate. But I hesitate to state that precisely seventeen years are required after the beginning of the fall of the curve of infectious diseases before a beginning of the rise of the circulatory curve may take place. I should in any case, just now, be at a loss to suggest a proper explanation for the occurrence of exactly this interval. Perhaps the collection of the reports on which these curves are based was open to too many errors of diagnosis or of recording to make valuable the inferences which the curves so clearly suggest. But it seems, taking the general movement of the two curves into consideration, that being saved from infectious diseases preserves the population for exposure to death from more chronic or, from the viewpoint of the aging process, more natural death. It would be rash, however, to assert that the second process begins seventeen years after the decline of the first.

Infectious diseases may be divided into two groups, in one of which are included tuberculosis and pneumonia, and in the other, the other acute infectious diseases, as is shown in figure 4. It appears, as a result of making this arbitrary division that if the acute infectious diseases had a share in bringing about the rise in the death rate of circulatory diseases, little influence may be attributed to pneumonia and tuberculosis, for the fall in the curve of these two diseases does not occur until later. It must, in consequence, be the other infectious diseases, represented in curve *A D*, which may be associated with the change.

These relations tell the story of the changes which took place in heart disease when compared with mortality in general and with certain acute infectious diseases, but they do not suggest its relative im-

portance in connection with other major causes of death such as pulmonary tuberculosis, pneumonia and cancer.

How heart disease increased during the twenty-year period from 1900 to 1920, how the rate from pulmonary tuberculosis fell, how the rate from pneumonia has not reached that of heart disease since 1910



Diseases grouped as follows:

A-(Infectious diseases)
- Typhoid fever
- Measles
- Scarlet fever
- Whooping cough
- Diphtheria
- Influenza
- Mumps
- Dysentery
- Acute poliomyelitis
- Meningococcal meningitis
- Malaria
- Cholera nostra

B-
- Tuberculosis
- Pneumonia
- Broncho-pneumonia

C-(Circulatory diseases exclusive of acute cardiac diseases)
- Apoplexy
- Angina pectoris
- Other diseases of the heart (including endocarditis)
- Diseases of the arteries
- Other diseases of the circulatory system

D-(Acute cardiac diseases)
- Pericarditis
- Acute endocarditis and myocarditis

States included: Connecticut, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island, Vermont, and District of Columbia.

FIG. 4. Mortality rates per 100,000 of various diseases in first ten registration states plus D.C. 1868–1925.

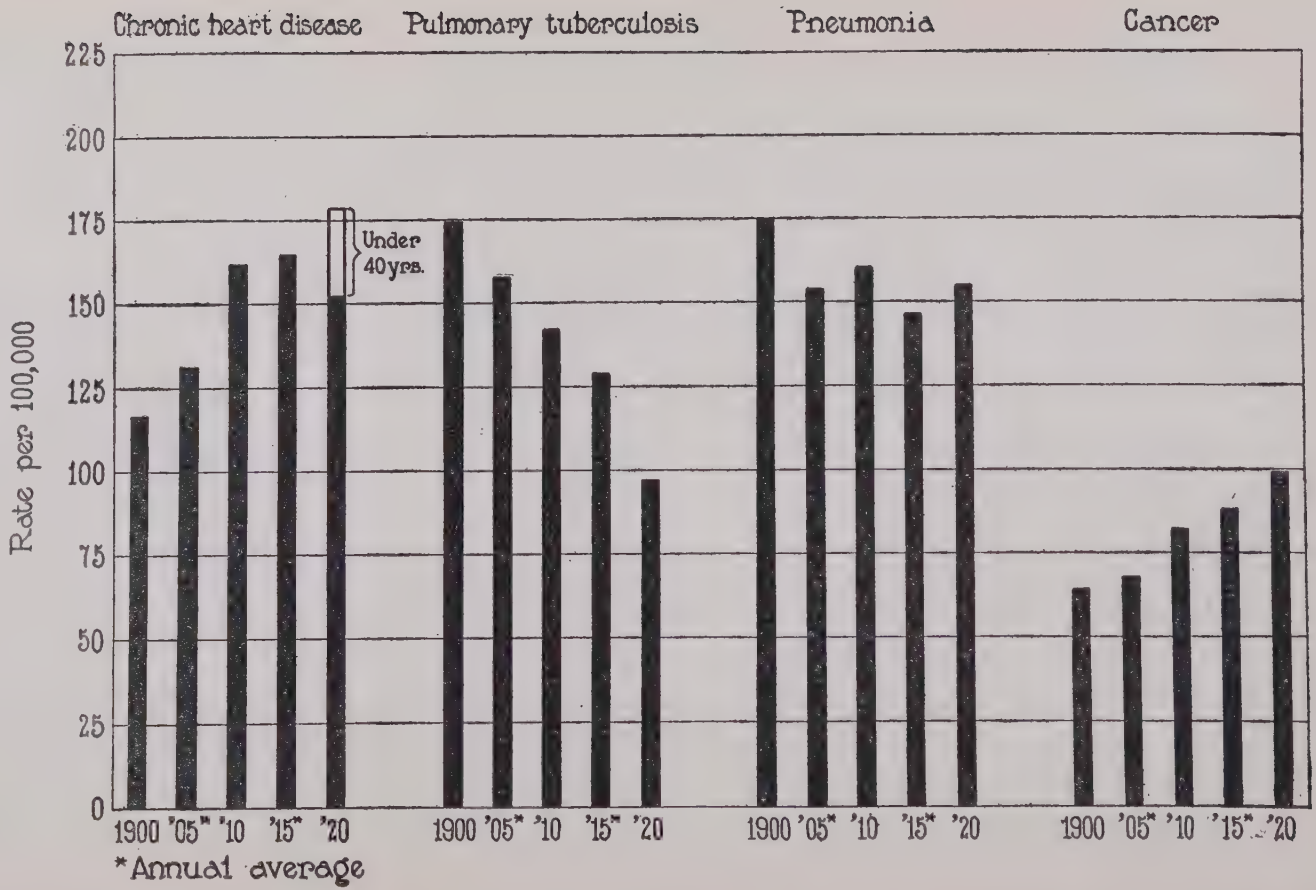

Chronic heart disease
Pulmonary tuberculosis
Pneumonia
Cancer
Rate per 100,000
225
200
175
150
125
100
75
50
25
0
Under 40yrs.
1900 '05* '10 '15* '20
*Annual average

FIG. 5

and how cancer is mounting, but is even now relatively speaking a small problem numerically compared to heart disease is illustrated in figure 5. One detail is indicated here to which I wish especially to direct your attention. You will find it in the heart disease group in the 1920 column. The point I refer to is that of the total death rate the proportion which occurs under the age of 40 is relatively small, indeed only one-sixth.

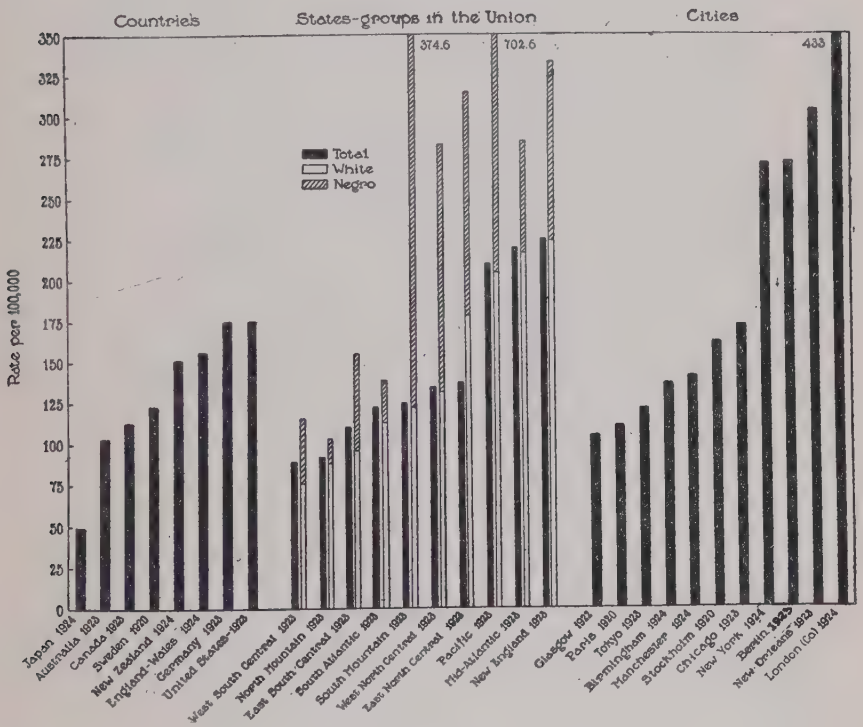


Fig. 6

That the high rates from heart disease which are encountered in the United States and in large cities like New York are not characteristic of this country, a comparison with other nations and with other cities makes clear. (See fig. 6).[4] In studying data such as those I

[4] I am indebted to Miss Claire Lingg of the Heart Committee of the New York Tuberculosis and Health Association for the data in this figure.

am about to present, I must repeat the warning that they do no more than suggest what sort of information should be available, that they are indeed removed from the possibility of being accurately representative. This state of affairs is, of course, deplorable; one of my purposes, however, consists in indicating how inadequate the data are and how important it is to suggest the directions in which improvement is desirable.

For the year 1923 the rate in Germany, 175 per 100,000, is the same as that in the United States. England and Wales and New Zealand are not far removed. If there were time it would be interesting to discuss the low rate in Japan.

A consideration of the rates in the cities shows that although that in New York is not far removed from the median, and that that in Berlin, New Orleans and London all show higher rates, its rate as well as that of these cities is greater than that of the United States Registration Area. The same observation applies to Berlin and London in respect to Germany and to England and Wales.

The question has often been raised whether latitude and longitude and climate influence the incidence, and in consequence the death rate from cardiac diseases. In the United States, if a report is made according to the geographical division of the States, it appears that the Southern and Mountain States at the left of the middle group of columns, present distinctly lower rates than the Pacific, New England or the Middle Atlantic States as is shown in figure 6. Similar relations are obtained by comparing death rates from *rheumatic fever* rather than from heart disease in various countries. (See table 1 (2).) I must point out, however, that to quote death rates from rheumatic disease is very different from quoting death rates for heart disease; for, although especially in the younger age groups, rheumatic fever is a common cause of heart disease, there is no fixed ratio between its occurrence and the number of individuals who develop heart disease.

It appears, for example, that the rate from rheumatic fever is especially low in the Straits Settlements, Honduras and Jamaica, but high in New South Wales, England and Wales and Ceylon. In the Straits Settlements, Honduras and Ceylon the rates are calculated on the basis of the whole population, whereas in Jamaica on that of Europeans only. In the British colonies the low rates in the

TABLE 1

Rheumatic fever in various countries and cities. Death rate per 1,000 deaths*

STATION	YEAR	RANGE OF YEARS	RATE PER 1,000 DEATHS	AVERAGE RATE	RANGE				
					Rate		Year		
					Maximum	Minimum	Maximum	Minimum	
1. Straits Settlements	1904		0.27						Whole population. All nationalities
2. Honduras	1903		1.01						Whole population
3. Jamaica	1903		1.64						Europeans only
4. N. S. Wales	1903		4.48						
5. England and Wales	1903		4.62						
6. Ceylon	1903		6.78						Whole population. All forms of rheumatism
1. Denmark		1894–1903		1.10	1.42	0.71	1897	1902	
2. Italy		1894–1902		1.21	1.38	1.06	1899	1894	
3. Prussia		1894–1902		2.37	2.57	2.22	1902	1898	
4. Norway		1894–1903		2.86	3.11	1.98	1902	1898	
1. Paris		1901–1903		1.91	2.14	1.75	1903	1902	
2. Christiania		1894–1904		2.35	3.55	1.29	1903	1904	
3. Berlin		1894–1904		2.38	3.53	1.42	1900	1894	
4. Copenhagen		1894–1904		3.23	5.02	0.92	1897	1902	
5. New York City and Brooklyn		1899–1904		3.48					

* From W. S. Church. Rheumatic Fever. Allbutt and Rolleston's System of Medicine, ii, 594–645 (2).

tropics may of course in part be due to the British custom of sending children to school in England at just those years at which the incidence of rheumatic fever is highest.

In connection with locality there seems good reason for believing that rheumatic fever is more prevalent in Boston (295 cases or 1.85 per cent of admissions to the Peter Bent Brigham Hospital) than in Oklahoma City (14 cases or 0.1 per cent of admissions to the State University and to St. Anthony's Hospitals (3)). In the same cities

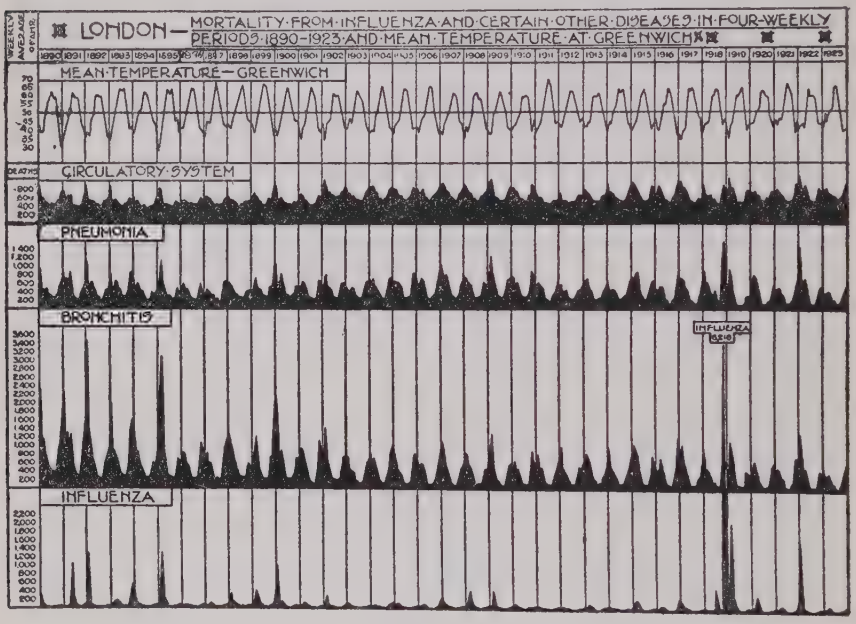


FIG. 7

and hospitals mitral stenosis, a disease which is post-mortem easily distinguishable and is regarded as a peculiarly characteristic rheumatic disease, occurred in 4.69 per cent of 1,362 autopsies and in none of 383 autopsies respectively. A similar observation has been published on the difference between the University of Virginia Hospital and the Massachusetts General; in the former chorea and rheumatic fever represented 0.7 per cent of admissions, in the latter 1.3 per cent (4). In comparison, however, with all these figures it is striking that

in Northern countries, such as Denmark, Italy, Prussia and Norway the rates are almost as low as in the tropics. And in point of fact, as great a range in rates is found in the northern cities in Europe and in the United States. The influence of latitude in any case is not clear and requires further and more detailed studies. In this connection the influence of season on deaths has also been explored. In London, for example, the seasonal influence on heart disease has been studied over a period of many years (fig. 7). It appears in the second curve quite clearly that in the winter months the number of deaths uniformly rises, synchronously with those of the respiratory infections, but curiously enough not with those of influenza.

In New York a similar record has been kept since 1914. (See fig. 8.) The curves from the point of view now being considered resemble those of London but show a closer relation between deaths from heart disease and from influenza. There are added here curves for tuberculosis and for cancer.

So far, I have dwelt on the place of heart and circulatory diseases in their relation to mortality. The matter is difficult enough to analyze from this angle. But it should be analyzed also from the point of view of morbidity. Here the difficulties, however, increase. I need scarcely point out that I refer to such matters as inaccuracy in diagnosis and incomplete and erroneous reporting, not to mention differences in definition and in classification which are used in various localities. On the whole, though, these diseases are so characteristic that they do not easily escape detection, and the custom which has been introduced of reporting in accordance with the International List of Causes of Death has reduced the trouble, and has made it possible to place reliance upon the published figures. From a study of certain morbidity statistics the great importance of the heart diseases also emerges. Data may be drawn from sources so varied as the draft in the United States and in England during the Great War; from statistics such as those of life insurance companies and of the British Insurance Act; from occupations, such as that of newsboys; from the incidence of heart disease in schools, both here and abroad; as well as from hospital statistics. (See table 2.) Clearly these are in each case samples only, of the population which need not necessarily be characteristic as Greenwood and Thompson (6) point out in the case of hos-

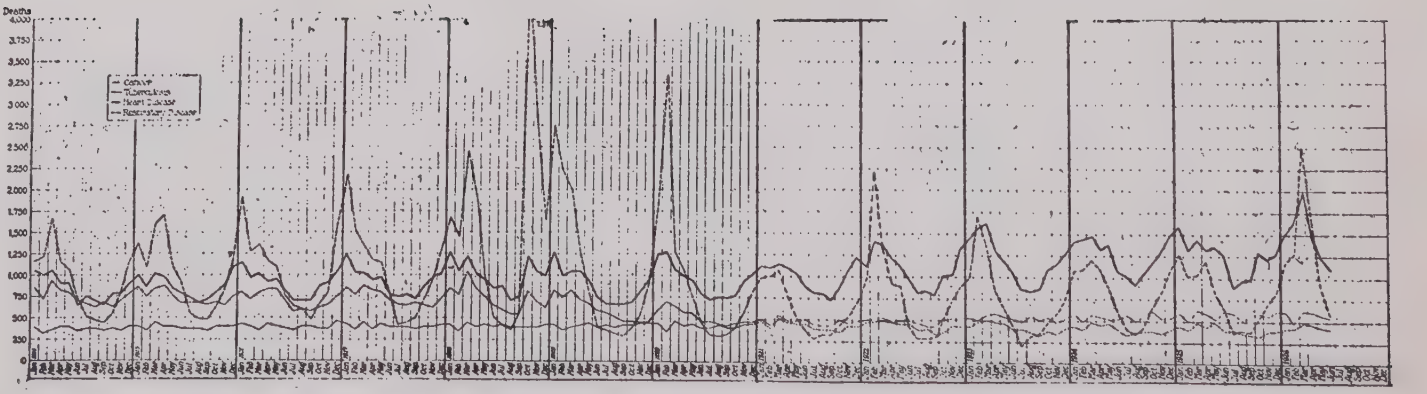


FIG. 8. Mortality in New York City from chronic heart disease, all respiratory diseases, cancer and pulmonary tuberculosis.

pitals. For the moment, however, data such as these represent the most reliable sources of information. We begin to emerge from a time, not long back, when hospital statistics were the staple in this field. In the United States draft during 1918, of 2,510,791, 85,143 men or 26.26 per 1,000 were found to have valvular disease of the heart. Among Scottish troups, during 1916–1917, "whilst still fairly representative" the rate was similar, being 24 per 1,000. Among 1,000 recruits examined for the United States army at New York City in 1926 (8) the rate was 15 per 1,000. Data are quoted by Miller to show that there is a difference in incidence between country and city. In the Channel Islands, among recruits in 1901–1910, the rate was 1.0 per 1,000, as against 32.4 per 1,000 in the East Riding, Yorkshire. And in Wales, during the Great War, among youths 18 years old, the rate in Carmarthen was 2.0 and in Cardiff 22.0 per 1,000. In the United States, on the other hand, such striking differences are not discernible. There is no difference between agriculturists and manufacturers in the North, but there is a higher incidence in the North, as a whole, than in the South; and the rate among negroes in the South is higher than among whites.

Dublin gives 20 per 1,000 as the number of persons rejected each year by the life insurance companies on account of heart disease, whereas, Hoffman puts the figure as 24.4. In a report recently made by the Ministry of Health for England and Wales when 10,476,000 people between 16 and 44 years of age appeared on the panel, it was estimated, on the basis of actual attack rates, that 15,912 might develop rheumatic heart disease if the rate were 1.51 per 1,000, as it appeared to be. There is apparently a great difference between the rate in the companies and that on the panels. It must be remembered that the former is, in a sense, an unselected, the latter a selected sample of the community.

In industrial workers, in general, and in the investigation of garment workers in New York it was found by Schereshewsky (14) that the rate was 20 per 1,000. Robinson and Wilson (15) arrived at the same figure in various industries in Cincinnati, and in a study of food handlers in New York, by the Department of Health (Harris and Dublin (16)), found exactly the same figure. In newsboys in New York,

TABLE 2

Morbidity. Chronic valvular disease. Various places. Various groups

LOCATION	YEAR	POPULATION INVOLVED	HEART DISEASE		REFERENCE
			Number	Per 1,000	
				per cent	
Troops:					
United States Draft	1918	2,510,751	85,143	26.26	Love and Davenport, 1919 (7)
Agriculturists:					
United States Draft, North, White	1917–1918	10,005		34.15	Love and Davenport, 1919. Table 142, p. 281 (7)
United States Draft, South, White		10,571		24.60	Love and Davenport
United States Draft, South, Negro		5,239		29.07	Love and Davenport
Manufacturing:					
United States Draft, East		7,934		35.56	Love and Davenport
United States Army	1926	1,000	15	15.00	Munly. Personal communication (8)
Scotland	1916–1917	10,000	243	24.00	Report No. 23. Ministry of Health, 1924 (9)
Channel Islands	1901–1910			1.0	Kennedy (10)
Yorkshire, East Riding	1901–1910			32.4	
Wales, Carmarthen				2.0*	R. Miller. From report on physical examination of men of military age. Vol. i, p. 154. London, 1920 (11)
Wales, Cardiff				22.0*	
Insurance:					
Metropolitan Life Insurance Company				20.0†	L. I. Dublin, 1925 (12)
Prudential Insurance Company	1915–1918			24.4†	F. L. Hoffman, 1920 (13)
England and Wales	1922	10,476,000‡	15,912‡	1.51	Report No. 23. Ministry of Health, 1924 (9)

Industry:					
Garment workers				20.0	Shereshewsky, 1920 (14)
Various (Cincinnati)				20.0	Robinson and Wilson, 1920 (15)
Food handlers				20.0	Harris and Dublin (16)
Newsboys—New York City	1925	1,078	15	15.0	N. Y. Tuberculosis and Health Association, 1926 (7)

* At age 18.

† Of persons who apply for insurance.

‡ Of persons actually insured. This equals the estimated number at ages 16–45.

TABLE 3

Morbidity. Chronic valvular disease. Various places. School children

LOCATION	YEAR	POPULATION INVOLVED	NUMBER	RATE PER 1,000						REFERENCE
Lanark		32,000		3.2						G. A. Allan, 1926 (18)
Philadelphia		23,671		6.3						Bd. Pub. Ed., 1924 (19)
Transvaal		30,000		7.0						L. Leipoldt, 1920 (20)
Glasgow		240,000*		7.0						G. A. Allan, 1926 (18)
Hempstead				8.2						L. Leipoldt, 1920 (20)
Staffordshire		70,138		9.6						L. Leipoldt, 1920 (20) (quoted from Priestly)
Aberdeenshire				10.0						G. A. Allan, 1926 (18)
England and Wales		366,000		10.0						Report No. 23. Ministry of Health (9)
Glasgow				10.0						G. A. Allan, 1926 (18)
Edinburgh				13.0						G. A. Allan, (18)
New York City		250,000		16.0						S. J. Baker, 1921 (21)
Germany				23.0						L. Leipoldt, 1920 (20) (quoted from unspecified German statistics)
Bath				23.6						R. Miller, 1926 (22)
London	1923	197,327	5,208	26.0						Annual Report, London, C. C., 1923 (5)
London	1919	195,162	6,622	34.0						Report No. 23. Ministry of Health, (9)
Rochester	1924		2,400	40.0						A. D. Kaiser, 1926 (23)
				Entrants—5–6 years		Intermediate—8 years		Leavers—12–14 years		
				Male	Female	Male	Female	Male	Female	
Glasgow				5.0				10.0		G. A. Allan, 1926 (18)
Bath		8,000		10.0				23.6		R. Miller, 1926 (22)
London	1919	195,162	6,622	25	22	33	36	38	49	Report No. 23, Ministry of Health (9)
				Total 34						
Rural	1924	100,000						2.6		R. Miller (quoted from Annual Report of Chief Medical Officer, Board of Education, 1924. London, 1925, 35). B. M. J., 1926 (22)
Residential								5.9		
Industrial								8.0		

* Includes Aberdeenshire and Edinburgh.

studied by the New York Heart Committee, the rate was 15 per 1,000 (17).

Lower rates are found among school children. (See table 3.) But this is not surprising for the ages involved are lower. Although the age of maximum incidence of rheumatic fever is 5 to 7, all children destined to suffer from chronic heart disease have not yet become affected, nor indeed does rheumatic fever take its entire toll at so early an age. Even before the age of 15, it makes a difference whether the rates refer to entrants or to leavers; that for leavers in Glasgow, Bath and London being twice as great as for entrants. In England there appears to be a difference also in school children between country and city, for the rate in the rural population is 2.6 per 1,000 and in the industrial 8.0, in a sample of 100,000 school children about 13 to 14 years old.

It appears, then on the whole, that among recruits, applicants for Life Insurance and in Industry, the incidence of chronic heart disease ranges from 15 to 35.56 per 1,000, the average being 20.8. There seems, moreover, to be a difference so far as locality and industry are concerned, for Kennedy gives the rate as low as 1 per 1,000 in the Channel Islands, against 32.4 in East Riding, Yorkshire; and in a country district in Wales as 2 per 1,000, against 22 in Cardiff.

Among school children the range of affection appears to be uncommonly wide, from 3.2 in Lanarkshire to 40 in Rochester, New York. Although the range is wide, in the 16 localities 9 fall between 7 and 16; two below, and five are above these figures. It seems to be so great as to render unlikely the possibility of extracting from its consideration unified results, and the criteria for diagnosis fixed and well observed.[2] It is necessary to be quite certain that the methods of examination were uniform and the criteria for diagnosis fixed and well observed before it is possible to regard the data with confidence. Not to do so would cause the inference to be drawn that heart disease and its contributing etiological factors were prevalent in and affected the several school populations in variety and in numbers too widely different. I refrain, therefore, from averaging results, apparently so dissimilar.

There appears the fact, then, from a consideration of all the morbidity figures quoted so far that roughly 20 per 1,000 individuals are affected with heart disease in the adult population in the United

States. Among school children so narrowly limited a rate cannot yet be given. The adult morbidity figures, however, harmonize even when obtained from such various sources. Is there a correspondence between the morbidity and mortality rates? If the figure for the death rate for 1920, in ages below 40 is recalled, it was found to be 26 per 100,000; the morbidity rate in the draft was 26 per 1,000; Hoffman's figure for rejections from the Prudential Insurance Company is not far removed from this; that in the industries; namely, 20 per 1,000 is somewhat lower. On the whole the morbidity rate is 100 times greater than that of mortality. In school children the morbidity rate in certain localities corresponds with the adult rate, though it is in general much lower. It remains for further investigation to smooth out these disparities.

If we turn now from morbidity statistics of the population at large to consider the number of cases of heart disease which actually arise in medical practice the following figures are discovered. I confine myself to England and to the United States. In the London Children's Hospitals (24) the per cent is 31; Miller (25) gives 38 per cent; Church (2) 57.5; St. Lawrence (26) 61; Ingerman and Wilson (27) 69; Cohn and Swift (28) 94. If there are, according to Swift (29), 175,000 cases of rheumatic fever in the country, and if the average of 65 per cent (an average of St. Lawrence's and Ingerman's and Wilson's rates) of cardiac involvement is accepted for the moment, there should be 113,750 cases of rheumatic heart disease. On the basis of the death rate, one-sixth of the cases of heart disease die under 40. Of the age of 40, there will be a discussion presently.

On the assumption that all cases of rheumatic heart disease, and only cases of rheumatic disease die under forty, a not unreasonable assumption, since the cases of syphilis under forty probably balance the cases of rheumatic disease above forty, the total cases of heart disease, seeing that the rheumatic ones number 113,750, should be 6 times as many or 682,500. But the figure usually given for heart disease in the United States is 2,000,000, an estimate which is supported by having found the rate in various circumstances to be 20 per 1,000. There is then a serious error, a difference between 2,000,000 and 682,500 in the assumptions. Or again, if there are 113,750 cases of rheumatic heart disease, they represent only 5.7 per cent of the estimated total of

TABLE 4

Distribution of muscular and valvular diseases of the heart in relation to age 40

MORBIDITY	NUMBER	BEFORE AGE 40	AFTER AGE 40	
		per cent	*per cent*	
Syphilis	91	13.6	86.4	Romberg (30)
		16.3	83.4	Wyckoff and Lingg (31)
		29.3	70.7	Stokes (32)
		Av. 19.7	Av. 80.1	
Arteriosclerosis	234	0.4	99.5	Wyckoff and Lingg (31)
Muscular degeneration	723	11.6	87.0	Romberg (30)
	Total 957	Av. 6.0	Av. 93.2	
Valvular heart disease	399	59.2	40.8	Romberg (30)
	670	73.68	27.32	Romberg (30)
	210	63.55	37.25	Schnitt (33)
Rheumatic heart disease	449	83.2	16.8	Wyckoff and Lingg (31)
	201	68.5	31.5	Fatianoff (34)
		65.3	34.7	Leuch (35)
	494	95.6	3.8	Church (2)
Rheumatic heart disease and chorea	191	94.3	5.7	Mackie (36)
	Total 2,614	Av. 75.41	Av. 24.73	
Mortality—organic disease of heart		14.6	85.4	International list of causes of death No. 90

2,000,000; whereas, it is known that one-sixth or 15 per cent of the cardiac population dies before the age of 40. The disagreement between 5.7 per cent of rheumatic cardiac cases and 15 per cent of cardiac deaths before 40 is great. If total cardiac disability were 1,000,000 instead of 2,000,000, rheumatic cardiac patients would represent 11.3 per cent instead of 5.7 per cent of the total and would approach the figure for deaths under 40, namely 15 per cent more closely. Just now it is impossible to say whether the error is due to too small an estimate in the number of rheumatic cases, to placing the involvement of the heart in rheumatic fever at too low a figure, or

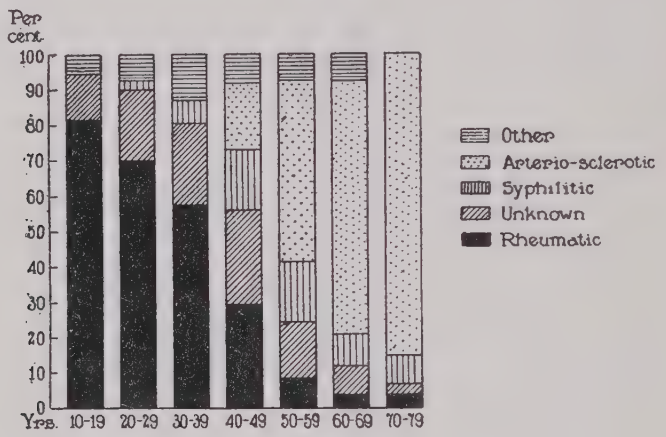


FIG. 9

perhaps to too high an estimate of the number of persons believed to suffer from heart disease.

The next problem, after having outlined from mortality and morbidity statistics what might in all probability be the incidence of heart disease in the community, concerns the distribution of the cases affected both according to *age* and according to *etiological* groups. To make an analysis according to age, commends itself especially on account of what has already been learned of the rising tide of chronic diseases which are naturally associated with older age groups (table 4 and fig. 9).

If, for instance, age 40 is taken as a dividing point, it appears that in syphilis 19.7 per cent of the cases are under 40 years of age, whereas

80.1 are over. And if 957 cases of degenerative heart disease are considered, again with the age of 40 as the dividing point, 6.0 per cent occur before the age of 40 and 93.2 above. Syphilis and the degenerative diseases combined lie above 40 to the extent of 86.6 per cent. If, however, instead of muscular or degenerative diseases we study 2,614 cases of valvular disease, 75.41 per cent occur under the age of 40 and 24.73 per cent above this age. From the point of view of mortality rates, the age of 40 seems likewise to be a useful point of division, for here it will be remembered 26 per 100,000, or 14.6 per cent of the total cases die before the age of 40 in a total death rate of 178, a ratio of 1 to 6.85. There appears now to be a difficulty like that which was encountered before, for these facts seem to indicate that 33.70 per cent (the average 19.7 + 6.0 + 75.41) of clinic patients, both in Germany and in the United States and in England, are less than 40 years old, whereas the mortality rate below 40 is only 15 per cent. The reason for this difference, as before, is difficult to understand. Wyckoff and Lingg have attempted to explain it; I shall return to this point later.

The age distribution then appears to give a clue to the nature of the diseases with which we must deal. It appears that the valvular diseases are predominantly the diseases which occur before the age of 40, the muscular diseases and syphilis afterward.

There is another way of approaching this matter of the division at the age of 40. It is well known that infection from rheumatic fever has its point of maximum incidence before the age of 10. It is true that this age is variously given, being placed at $6\frac{1}{2}$ (Ingerman and Wilson (27) and at 7 (Miller-Poynton, quoted by Ingerman and Wilson (27)). But that the turn of the first decade of life is the important one from the point of view of onset is seen also by the sharp rise in incidence that takes place between entrants and leavers in British schools.

Infection due to rheumatic fever occurs, of course, at other age groups, but it is here at a maximum. Church (2) in a study of 943 cases of rheumatic fever, gives the age incidence under 10 as 13.99 per cent; under 20, as 57.57 per cent; and under 30 as 83.23 per cent. It is difficult to assign a figure to represent accurately the duration between onset and affection. There seems to be relatively speaking a

small amount of data on the subject. But Coombs (37) states it as a fact that 66 per cent of cases of heart disease following on rheumatic fever occur between the ages of 5 and 15. Thayer (38) gives the same percentage below 20. Mackie's (36) cases, below 20, were 55 per cent. St. Lawrence (39) cites the history of 7 cases in which rheumatic fever preceded the detection of valvular disease at intervals ranging from 13 to 72 months. The figures for the 7 cases are 13, 26, 41, 45, 53 and 72 months; the average being 41.6 months. In the seventh case, heart disease was present before the appearance of the more usual rheumatic symptoms. Among 25 cases of mitral stenosis, Mackie reports that the lesion was developed in 24 months in 22, but that it required $5\frac{1}{2}$, $6\frac{1}{2}$, and $5\frac{2}{3}$ (chorea) years in 3 additional cases. It may take then 1 to 6 years for the cardiac lesion to form. Meanwhile manifestations of rheumatic disease may be quite absent. Next, the length of time before heart failure begins, Romberg (30) gives as approximately 7 years in 102 cases of valvular heart disease in his Leipzig clinic. The stage of heart failure itself may on the average last, as he shows also in a study of 172 cases in the Leipzig clinic, 4.8 years. If now these three periods are summed up, (*a*) the period from the beginning of the infection to the establishment of the chronic valvular lesion, say 1 to 8 years, the average about 4 years; then (*b*) from this point to the onset of heart failure, say about 7 years; and finally (*c*) from this point to death, say about 4 years, the total period is somewhere in the neighborhood of 15 years. On the assumption that Church's figures and those of Ingerman and Wilson (27), and of Miller and Poynton are correct, and that the ages 5 to 15 embrace the usual period for infection from rheumatic fever, the total course of the disease will have been run by the ages 20 to 30 years. Or, if the higher figures in Church's table are to be considered, namely, those which assign 25 per cent of cases of rheumatic fever to the third decade, the 20 to 30 years age group, the disease will have run its course between the ages of 35 and 45. This calculation again permits the selection of the age of 40 as an important point in a consideration of chronic heart disease, for it has now been shown that this age is significant in the natural history of rheumatic fever, that it is, moreover, important in morbidity and mortality statistics.

In view of the great significance that rheumatic fever has in the early

ages of life, it becomes important to obtain some estimate of the number of cases in a population which suffer from this disease. Reference has already been made to Swift's (29) statement that there are 175,000 cases in the United States. To obtain data for this is difficult, for rheumatic fever has rarely been a notifiable disease. There was a period, however, from 1891 to 1895, when the disease was notifiable in Norway (table 5). At that time it was found in a population of

TABLE 5

Incidence of rheumatic fever. Norway—English and Welsh practitioners—City of Ulm*

	YEAR	AGE	POPULATION		ATTACK RATES PER 1,000		CASES	
			Males	Females	Males	Females	Males	Females
Norway	1891–1895†	15+	604,257	698,041	2.07	1.9	6,281	6,771
			Total 1,302,298‡				Total 13,052§	
Practitioners	1922	16–24			1.995			
Ulm	1883–1900	10–20			1.93			
Practitioners	1922	All	57,998	32,893	0.88	1.76††	51	58
			Total 90,891**				Total 109	
Ulm‡‡	1906	All			1.75	1.24		

* Compiled from pages 64–65, Reports on Public Health and Medical Subjects. No. 23. Ministry of Health, 1924 (9).

† Years of compulsory notification.

‡ 64.4 per cent of total population of 2,020,840; 1900 Census.

§ Aged 15+ was 81.7 per cent of total notified (15,978).

** Total population at risk 12,633,000.

†† Females equal twice the males. Half the females at susceptible age, 16–24.

‡‡ F. Prinzing. Handbook Medical Statistics, 1906, p. 340.

2,020,840, (1900 Census) that among 1,302,298 (64.4 per cent) above the age of 15, 13,052 cases developed. The male population was 604,257, the attack rate 2.07 and the cases of rheumatism 6,281. The female population was 698,041, the attack rate 1.9, and the cases 6,771. The average attack rate equals 1.98. In the Practitioner's Enquiry carried out under the Ministry of Health (9) 90,891 persons came on the panel in a certain selected portion of England and Wales,

of a population of 12,633,000. Among these 51 males and 58 females developed the disease. The attack rates were 0.88 for males and 1.76 for females. For the age period 16 to 24, approximately like that in the Norwegian data, the attack rate was 1.995. There are figures for the city of Ulm during the years 1883 to 1900 which give attack rates for the ages 10 to 20 as 1.93.

Swift (29) on the basis of mortality data for 1916 in the United States Registration Area, says that the combined figures for rheumatic infection show a rate of 6.7 per 100,000. If, as he believes, the death rate represents 4 per cent of the cases affected there should be in the United States between 150,000 and 175,000 cases of rheumatic fever. On the same basis, the death rate being 6.7 per 100,000, and representing 4 per cent of the cases, the attack rate in the United States equals 1.67 per 1,000. It will be seen then that a comparison of the attack rates of the Norwegian, Ulm and Practioner's Enquiry presents a certain degree of correspondence; the Norwegian figure for both sexes being 1.98 (all ages above 15), the British figure being 1.32; the Ulm figure being 1.45, and Swift's 1.67.

It is not my purpose to discuss all the factors which make for the occurrence of rheumatic fever. The problem of possible bacterial agents has, as you know, engaged the attention of investigators for many years. I need go into no further detail than to recall the fact that there is no general agreement on which microörganism is the efficient cause, nor indeed whether the cause is a microörganism at all.

The relation of damp and wet and cold is also often mentioned, especially in the older literature. There are two aspects of this phase of the problem, seasonal and geographical. It has been explored by many older writers, reviewed carefully by Pribram (40) and more recently by Newsholme (41), Greenwood and Thompson (6), Young (42), (43), the Practitioner's Enquiry (9), and Miller (11). Pribram, Newsholme, and Greenwood and Thompson have opposed the idea of a relation of rainfall to the occurrence of rheumatic fever; Garrod (44), on the whole, favored it, as did Young, the Practitioner's Enquiry and Miller. Opinion then is still divided. Miller (22) reports that of 196 cases, 122 or 62.2 per cent occurred in damp rooms. He presents data to show that among persons who live in them or in basements or in ground floor rooms without cellars, the

liability to the disease increases. The Practitioner's Enquiry (9) concludes that dampness has a higher correlation with acute rheumatism than with any other rheumatic disease. It was also shown that if the attack rates from rheumatic fever and rheumatism of the heart for all England and Wales were placed at 100, the attack rates for Lancashire may be placed at 159, the highest in England. Norwich, in East Anglia, is on the contrary exceptionally free from rheumatic diseases. Lancashire situated in the Northwest, has relatively the higher rainfall.

Some day perhaps we may recall in this connection Pettenkoffer's idea that the height of the ground water in Munich was related to the occurrence of typhoid fever.

A discussion of rheumatic fever, however, is not complete without reference to the possibility of its infectious nature. Church (2) quotes Friedländer as having seen 12 cases in the same house in Leipzig in 3 years. He also quotes Edelfson as having counted 728 cases in 492 houses.

More recently a number of new reports have been published on its familial and hereditary aspects (table 6). Coombs (37) gives 50 per cent as the incidence in families, in which there were cases in addition to his patients. St. Lawrence (45), in a hundred families, gives the figure as 29 per cent for rheumatic heart disease; Miller (22) quotes Coates and Thomas as giving 47 and 37 per cent affected, in two series, and Morrison, as giving 48 per cent; Faulkner and White (46) give the rate as 35.5 per cent. In the control families of healthy individuals, the per cent falls to 16. In rheumatic families, if I may so call them, there were 8 to 10 per cent of exposed persons infected as against 1 to 2 per cent in the population at large, and in the families of healthy controls only 2.95 per cent. These figures are striking enough to stimulate more searching inquiry in this direction. It is a phase of the problem which was not without interest in the study of tuberculosis, and is now the subject of research in lobar pneumonia.

It is not surprising that with a disease incidence, as large as that in rheumatic fever, much thought has been expended on the possibility of remedying this situation. From the point of view of the public health to institute a serious effort in this direction is eminently desirable. On account of the frequent association of other affections

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TABLE 6

Rheumatic diseases. Familial and hereditary aspects

FAMILIAL	DISEASE	NUMBER PATIENTS	NUMBER STUDIED		NUMBER OF MEMBERS IN SAME FAMILY AFFECTED	TOTAL FAMILIES AFFECTED		AFFECTED PERSONS DISCOVERED		PERSONS UNAWARE OF DISEASE		REMARKS
			Families	Persons		Number	Per cent	Number	Per cent	Number	Per cent	
St. Lawrence (45)	Heart disease		100	480	2 or more	29	29	38	8*	27	71	*Usual 1–2 per cent
	Acute rheumatic fever	100	100	480	2 or more	24	24	49	10*			*Usual 1 per cent
	Chorea		100	480	2 or more	3	3	8	1.6			
Ingerman and Wilson (27)	Rheumatism	185				74	Parents 40					
						51	B and S† 28					
Miller (22)	Rheumatic infections	44				21						
(From Coates and Thomas)		32				12						
(From Morrison)		54				26						
Coombs (37)							50					
Faulkner and White (46)	Rheumatic affections	200	200	1,235*	2 or more	71	35.5	108	8.79			*642 examined
	Healthy controls	75	75	474	2 or more	12	16.0	13	2.95			*366 examined

HEREDITARY	NUMBER OF PATIENTS	PARENTS AFFECTED					SIBLINGS AFFECTED
		Number	Per cent	Fathers	Mothers	Both	
							per cent
Faulkner and White (46)		332	8.9				8.66
Report 23 (9):							
Males			24.0	13	21	8	
Females			43.0	7	15	2	

*Compare with statement on same line under remarks.

†B and S—Brothers and sisters.

TABLE 7

Tonsillectomy. Its effect on the occurrence of rheumatic manifestations

DATE	AUTHOR	NUMBER OF CASES TOTAL	WITH TONSILLECTOMY		NO RECURRENCE		WITH RECURRENCE		WITHOUT TONSILLECTOMY		NO DEVELOPMENT OF MANIFESTATIONS		WITH DEVELOPMENT OF MANIFESTATIONS		REMARKS
			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
	Complete tonsillectomy														
1908	Rosenheim (49)		10		10	100	0	0							
1911	Archibald (50)	7	7		5	71.4	2	26.8							
1915	Young (51)	21	21		6	28.6	15	71.4							
1917	Crewe, Watkins and Rothholz (52)	49	49		28	56.3	21	43.7							
1920	St. Lawrence (26)	85	85		54	63.5	31	36.5							
1923	Hunt and Osman (47)	144*	66		31	47	35	53	78		45	58	33	42	*All cases
		(99)*	(50)				(23)	(46)	(46)				(15)	(33)	*After first attack
		(48)*	(16)				(12)	(75)	(32)				(18)	(56)	*After later attacks
1924	Ingerman and Wilson (27)	167	70		17	24	53	76	97		19	19.6	78	80.4	
1924	Dulaney (53)		22		22	100.0	0	0							
1926	R. Miller (25)	133	45		18	40	27	60	(83)						
1926	R. Miller (A. P. Thompson) (48)	16	6		6		10	62.5							
1926	Mackie (36)	299	80		46	57.5	34	42.5	207		82	39.7	125	60.3	After first attack
			12		0	0									Before first attack
	Totals		483		255	52.8	228	47.2	382		146	38.2	236	61.8	
1926	Kaiser (23)	2,400	1,200						1,200				128		Rheumatism
	Partial tonsillectomy														
1921	St. Lawrence (26)	9	9		1		8								
1924	Ingerman (27) and Wilson	18	18		4		14								
	Totals	27	27		5	18.0	22	82.0							

more especially that of the tonsils with this condition attempts have been made to modify the incidence and course of rheumatic fever by attention to this source of infection. Unfortunately much information does not yet exist on the subject.

There are, however, several series of cases beginning in the year 1908 in which reports have been made on the effect of operation on the tonsils (table 7). It is perhaps important to distinguish the cases in which removal of the tonsils was complete, that is to say the cases in which the tonsils were completely enucleated and those in which the enucleation was incomplete. Three hundred and ninety-one cases were observed before and after operation. The rheumatic manifestations for which the operations were performed occurred in 49.6 per cent of these. This figure is low rather than high, for recurrence involves consideration of the period of time after operation during which observations were carried on, as it has been found that the percentage rises with time. This point is especially important, for in several instances enumerated in this table the duration of observation has been short, a matter of months rather than of years. In connection with these 391 cases, 2,400 cases studied by Kaiser (23) should be mentioned. It is unfortunate that Kaiser has not yet published analyses of his large number of carefully studied cases in such detail as to make it possible to enter the results in a table such as this. In order to be able to do this, it is of course necessary to be able to follow the course of the disease in each individual. Few investigators have as yet appreciated the importance of this method of presenting data, especially outside the United States.

In the group in which enucleation was incomplete there were 27, among these 22 (82 per cent) recurred.

There have been reported several groups of cases in which no operation on the tonsils was performed. These serve as controls. Of well studied cases, 175 may be mentioned, among which rheumatic manifestations developed in 111 or 64 per cent. The largest series of cases studied from this point of view is Kaiser's (23). Twelve hundred cases were observed. Of choreic manifestations there occurred 7, of rheumatic 128, and of cardiac 52. But among the cases operated upon there were 8 instances of choreic, 129 of rheumatic and only 44 of cardiac manifestations; that is to say there were more rheumatic

and choreic manifestations in those operated upon than in the so called controls. It is necessary to speak of manifestations rather than of cases, for the number of cases which the manifestations involved is not given. The most signal advantage of the operation seems to have been in the cases of tonsillitis, for here among the operated there were only 64 cases as against 586 in the non-operated. Unfortunately the effect of operation on the matter of recurrence, the essential object of study, is not deducible from Kaiser's report. On the whole then it cannot be said that the results of this therapeutic measure are satisfactory, recurrence taking place in 50 per cent of the cases. When series of cases reported by individuals are considered, attention must be paid to St. Lawrence's view (39) that, specially in cases in which chorea is not a factor, the performance of tonsillectomy is an extremely important measure. To discuss each series of cases is important, but impossible here. Miss Lingg, my associate in the Heart Committee in New York, is at present engaged in making a complete analysis. Interpretation is difficult, for not only, as has already been said, must time of observation be taken into consideration, but also the time of operation in relation to the onset of rheumatic disease and especially the relation to first or second attacks. Although, from Kaiser's observations, tonsillectomy seems to make no difference from important points of view, this method of therapeutics must nevertheless be carefully pursued precisely for the reason stated. It is urgently desired that observers record their cases in such a way as to make it possible to deduce what has actually been the course of events in their patients.

Of other means of preventing and relieving rheumatic fever, only a few words need be said. The use of drugs, as effective agents of cure, must unfortunately be dismissed. Careful investigators are unanimous in their opinion that no hope lies in the direction of the use of those which have so far been proposed.

But that, as in the case of tuberculosis, something may be accomplished by prolonged and complete rest, the reports of Swift (54) more recently published, indicate clearly. Coleman (55) has insisted on this point and has illustrated his contention with telling case reports. Experiences like these emphasize the fact that in order to duplicate them, facilities in the way of beds in hospitals and in convalescent institutions properly supervised are requisite. They tend also to lend

point to the general observation that treatment of patients in private, in the economically more self-sufficient walks of life, is attended by prolongation of activity and of life. That the failure to provide such facilities possibly shortens usefulness and life will appear in considering the curves of Wyckoff and Lingg.

Aside from the analysis which has already been made, showing the very partial success of tonsillectomy on the course of rheumatic infection, a study of the death rate curve in New York State made by Swift (54) shows that no substantial change has occurred in ages below 40, either in endocarditis or in pericarditis or in organic heart disease (figs. 10 and 11). His curves for rheumatism and for acute rheumatic

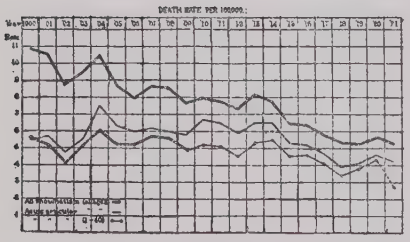


FIG. 10

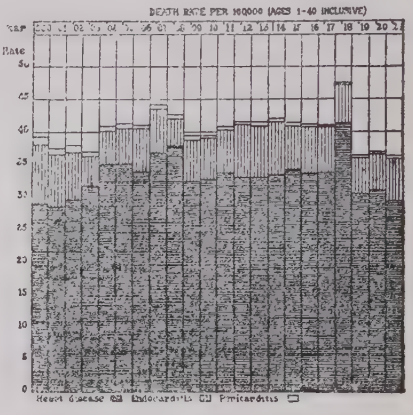


FIG. 11

fever show a persistent fall and encourage one in the pursuit of the therapeutic measures which have been described.

If we return now to consider the etiological groups which have contributed to the total of deaths after age 40, the largest number of cases are due to senescence. A certain number are found to be sequels of syphilitic infection. There are included, also, a number of cases acquired at this age of valvular heart disease and perhaps of muscular disease too, due to rheumatism and to a lesser extent to other infectious diseases, and a certain number due to infection acquired before this period. Arrival at old age brings with it certain disadvantages. It not only ushers in the natural probability of death by

a normal cardiac mechanism, but on account of the inherent defects of the system in advancing years, exposes individuals to injury, as Dublin (56) suggests to which they were earlier not prone. Exactly which these might be from the point of view of the circulatory system is not yet quite clear. But, if this system were so affected, a disease of old age, rather than old age itself, will have occurred; cases of this nature would perforce swell the cardiac death rate. But the overwhelming majority of cases must be due, if the considerations which have been urged are correct, to the cause just mentioned. It has already been shown that five-sixths of the deaths from heart disease occur after the age of 40. If these were due in large measure to muscular and vascular, rather than to valvular diseases, one would expect, if the muscular diseases were separated, to find a greater percentage of cases of this type after the age of 40. That this is actually a fact has already been shown (table 4). Of 957 cases, 93.2 per cent were 40 and over.

The duration of muscular disease of the heart has been studied by Romberg (30) in 176 cases in the Leipzig clinic. It was found there that the interval between the time when the first attack was experienced and when the heart began to fail averaged $14\frac{1}{2}$ months. The time between the beginning of heart failure and death averaged $5\frac{1}{2}$ months, ranging from a few days to 2 to 3 years. On this basis the total duration is put down as $1\frac{1}{2}$ to 2 years, ranging from a few days to 20 years. Cases were known to last as long as 10 to 14 and even 17 to 23 years.

That cases of syphilis also fall into this group, appears from the fact that 80.1 per cent occur after 40 (table 4). What the number of cases of syphilis is in the United States, and what per cent of these develop cardiovascular disease is very difficult to ascertain. I can find no adequate estimate of either group. In the Registration Area for 1920, the death rate for syphilis is placed at 9.1 per 100,000 population or 9,100 deaths. Stadler (57) puts the occurrence of syphilitic aortitis among syphilitic autopsies in the Leipzig Pathological Laboratory at 82 per cent. Hubert (58) gives the ratio of aortitis to visceral syphilis at 70 per cent. At this rate there would be 7,362 cases of syphilitic aortitis in the country, a rate of 7.36 per 100,000 population. In comparison with this figure, the incidence of syphilitic aortitis among

general autopsies is very high. Gruber (59, p. 96) gives the figure as 4 per cent (4,000 per 100,000 population), Lamb (60) as 4.58 per cent, Oberndorfer (61) as 6.89 per cent. In a revision of the Registrar General's Mortality Statistics by Osler (62), apoplexy, aneurysm and aortitis, organic diseases of the heart and diseases of the arteries, all told caused 92,564 deaths; of these 12,000, 12.9 per cent, were due to syphilis. In Bellevue Hospital (63) of all admissions in 1915, 30.5 per cent are said to be syphilitic. In certain industries in New York those infected are 22 per cent (63). Elsewhere in the country the rate falls as low as 7 per cent (63). Since the introduction of the Wassermann reaction, the number of cases in general medical clinics diagnosticated as syphilis has increased. In 1896 (Mengel (64), Leipzig) it was said to be rare; in 1919 (Adlmühler (65), Munich) it was put at 18 per cent and in 1924 (Wyckoff and Lingg (31), New York) at 8.6 per cent. Steinfield, Pfahler and Klauder (66) found it only in 11 per cent of syphilitic males, a low figure in a group which would generally be regarded as favorable for yielding a high figure.

The matter may be summed up in the following way:

Recapitulation

Mortality:

Syphilitic deaths—Registration area, United States	9.1 per 100,000
Syphilitic cardiac deaths are of all cardio-vascular deaths—Registrar General's Report	12.9 per cent
Of syphilitic autopsies, syphilitic heart disease represents	82.0 per cent
Of general autopsies, syphilitic heart disease represents	4–6.85 per cent

Morbidity:

Syphilis, general morbidity	7–30 per cent
Syphilis in general hospitals (Bellevue, New York City)	30 per cent
Syphilis in industries, New York City	22 per cent
Syphilis elsewhere in the United States as low as	7 per cent
Syphilis in syphilitic cardio-vascular cases equals	11 per cent
General cardio-vascular disease—syphilitic cardio-vascular cases equal	8–18 per cent

A low estimate places the number of persons in the country infected with syphilis at about 1,000,000. In choosing this per cent I am following the example of a Royal commission (32, p. 39). If 11 per cent represents the proportion that develops cardio-vascular diseases in a syphilis clinic, the number may be placed very roughly

at 110,000 cases. And if 8 per cent (Wyckoff and Lingg) is the proportion of syphilitic heart disease in a general clinic, the number of syphilitic cardio-vascular cases would be 120,000 on the assumption that the total number of cases of heart disease in the country is between

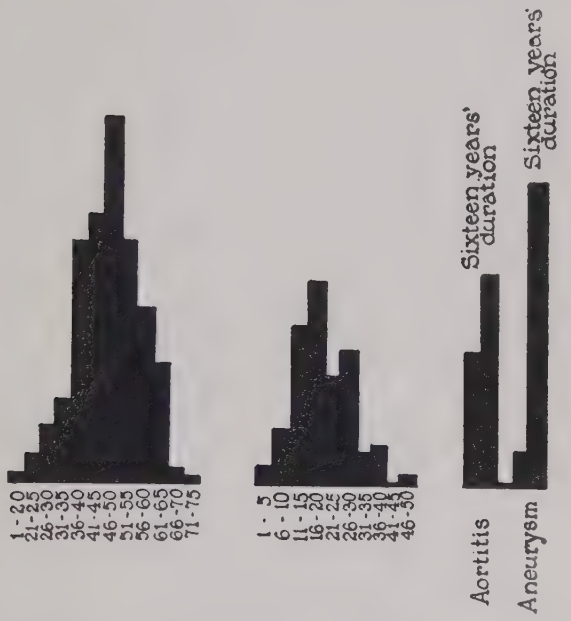


FIG. 12. In the figure to the left, the relative incidence of cardiovascular syphilis for various age groups is given. In the middle figure is indicated the relative number of cases in which the duration between infection and onset of symptoms equalled the number of years given below. To the right, the division between the long and the short columns in each case is sixteen years. Before sixteen years more cases of aortitis (and of aortic valvular insufficiency) are detected than of aneurysm. Aortic insufficiency has a shorter "incubation" period than aneurysm, apparent rather than real, because on account of its conspicuous physical signs it can be detected earlier than aneurysm. From J. H. Stokes (32).

1,000,000 and 2,000,000 cases. This agreement is fair, but it is based on the roughest of estimates and is entitled to no great confidence.

But it is more important now to try to find the age incidence than the actual number of cases of syphilitic heart disease.

Stokes (32) has arranged 190 cases in the curve to the left in 5-year age groups (fig. 12). He has not published a scale, but by measure-

ment I find that 10.9 per cent (24 cases) were below 35 years and 29.3 per cent (55 cases) under 40 years. A large majority then is above 40. In the middle curve he shows that few cases, relatively speaking, have an incubation period less than ten years; that in most cases this period lasts from 11 to 30 years, the greatest number, 16 to 20 years. If syphilis is acquired in the second and third decades, and if the time before the development of symptoms is usually about 20 years, the appearance of these would generally be expected about age 40. Mackenzie (1908) mentions a case (quoted by Romberg (30)) in which cardio-vascular phenomena were discovered 7 weeks after infection; but it is unusual to find them before 2 years.

If now the distribution of heart disease according to etiology and age groups is undertaken it is found that a curve expressing the sum of the cases of syphilis and of arteriosclerosis, which occur both in public and private practice falls far below the curve of morbidity which one should expect and which would run parallel with the mortality curve for these age periods. This statement applies to data collected not only in this country, but also abroad. Wyckoff and Lingg have studied this problem in some detail, and from their study follows a consideration of value for interpreting the data which come from the clinics for public patients, and perhaps also, but to a less extent, in private patients. These are the curves to which I have already referred. If it is true that the natural history of heart disease, whether from rheumatism, from syphilis or from old age, follows a usual course, then the curve of morbidity should follow the curve of mortality in some usual fashion. The curve of mortality must, within limits of course, be considered as the norm (fig. 13). In these curves, taken from Wcykoff and Lingg, the mortality for New York is given in the uppermost. Obviously the curves for ward patients and the curves for private patients do in some measure resemble the mortality curve, but the curve for public ambulatory patients and, of course, the curve of all ambulatory patients, public and private together, fails signally to resemble it. In the first place, the apex of the second mode of the public ambulatory patient curve is found to be 20 years before the apex of the mortality curve and 10 years before that of the private patient curve. The public patient curve, moreover, falls abruptly 10 years earlier than that of the private patient curve. Wyc-

koff and Lingg think, furthermore, that the first part of this curve is higher than it should be, because the numbers were augmented by the inclusion of patients brought to the Bellevue clinic from outside the Bellevue district, from the schools, and from social service sources

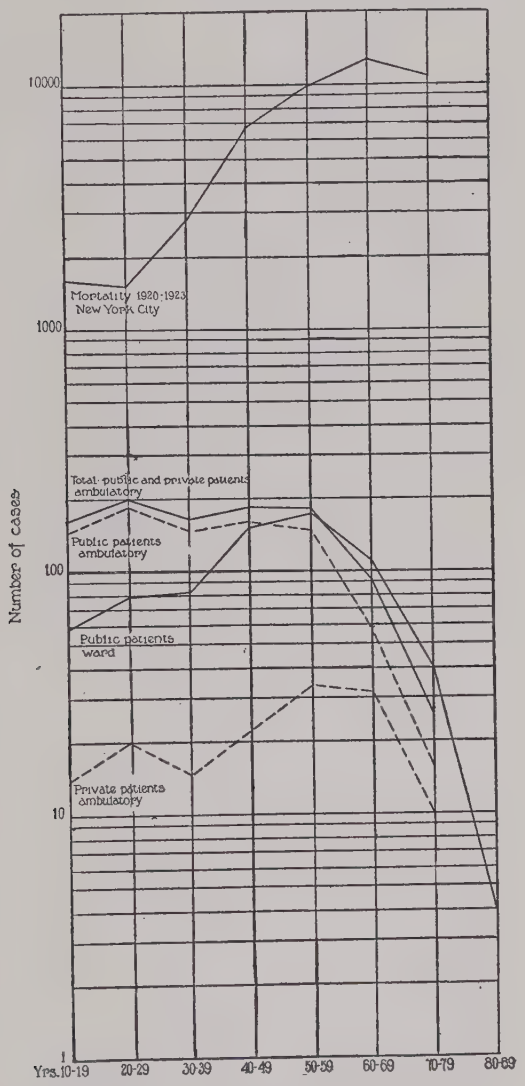


FIG. 13

not connected with the hospital. There results in consequence, a distortion of the curve which might occur elsewhere also. Why the second portion of this curve, that after the age of 40, fails to follow the mortality curve is, not clear. Indeed the matter is difficult to understand, but Wyckoff and Lingg suggest the following explanation. People come to the clinics in early years, because rheumatism is a dramatic disease and entails great suffering. The heart disease, which results from it, occurs when people are quite young and when the hope of a useful life is still strong. Accordingly they seek relief. The clinic curve is consequently high. Heart disease in the older age groups comes on insidiously. The meaning of the symptoms is misunderstood. The outlook in life is no longer full of promise. Economic pressure has been relieved, either on account of savings or because patients are supported by children or otherwise. The situation is one which in any case is anticipated as part and parcel of the gradual process of decay. Patents do not come to the clinic, they do not seek advice, they accept the inevitable. The clinic curve falls, precisely at the moment when one would expect it to be high. If this description represents the situation in public practice, the curve for private practice ought to differ from it, and in point of fact it seems to do so although it does not follow the mortality curve as closely as it might. But the experience here is small, and it is not beyond possibility that the argument which applies in public practice applies also in private. This is a subject which requires further and more detailed study. But in these considerations there is included a warning. Data obtained, especially from public practice, require scrutiny with the view to making certain that the samples offered as illustrative of the course of disease actually are so.

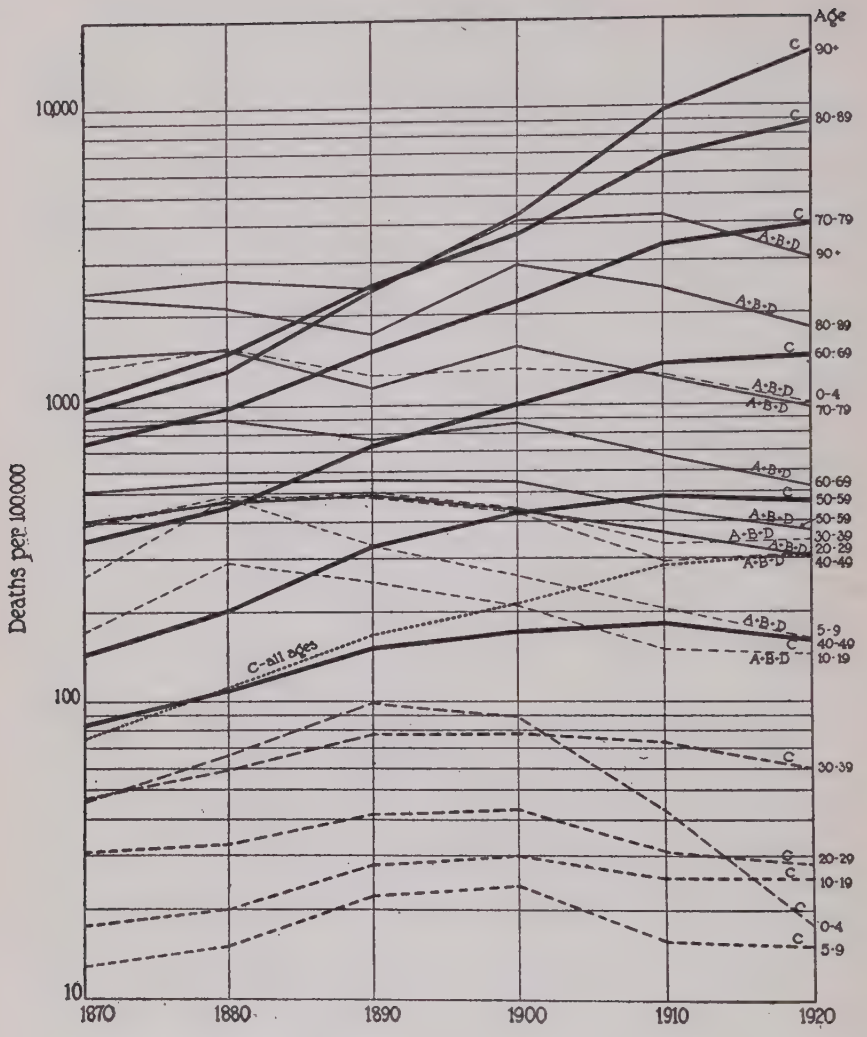
Of the bearing of race and of sex on the incidence of heart disease I propose not to deal. Their influence on the phase of the problem I am discussing is not sufficiently clear. That girls, at the age of puberty or to 20, according to Osler, or to 34 according to the Practitioner's Enquiry (9) fall subject to rheumatic fever twice as often as boys, though contrary opinions are also expressed, and that heart disease due to syphilis is more common in men, is well known.

It appears also to be a fact that the duration of life in negroes subject to heart disease is a decade less than among the white population.

The incidence of heart diseases among them seems to be greater everywhere in the Union, as is seen in the statistics of mortality when the State groups are studied; theirs exceeds the rate of the white population by 26 to 68 per 100,000 wherever their population is over 1,000,000. When it is small the rate rises, as it must, if the scale is per 100,000. The difference is assigned by Dublin (12) to the greater incidence of syphilis, malaria and typhoid fever. Higher rates in earlier age groups may naturally be due also to decrease in natural longevity.

I have laid so much stress on the age of 40 as a dividing point not only because, as it appears, the majority of cases before this period have their origin in infectious diseases and especially in the rheumatc group, but because I wish to emphasize the fact that these are, relatively speaking, a small number, namely one-sixth, of the total; that in point of fact, by far the greater number of deaths due to heart disease, namely, five-sixths occur after this period. On the far side of age 40, a certain number are the sequels of syphilis. But presumably the larger number results from what is usually called degenerative disease, viz., from arteriosclerosis. I wish to contend that these conditions are properly not diseases at all, but that they represent differentiation phenomena in the course of the ordinary growth process. Multicellular animals, and the argument need be suggested only, have, if not a fixed, at least an anticipated longevity. From the point of view of expectancy years have been added to life. Unfortunately this fact has sometimes been interpreted as being a biological, rather than an arithmetical phenomenon. There is sometimes confusion between the meaning of expectancy and of longevity. The duration of life has not been extended; on the contrary, the attainment of its natural length has merely been rendered possible. How this may have come about, at least in part has appeared in studying the relation between the declining death rate from infectious diseases and the rising one in chronic diseases (figs. 3 and 4). But the conclusion that the increased number of deaths from heart disease has occurred in the older age groups exclusively results from the study of specific death rate curves (fig. 14).

All the heavy dotted curves, marked *C* at the bottom of the figure, that is to say curves of heart disease, one for each decade *below* the age of 40 run to all intents and purposes a horizontal course. The



Diseases grouped as follows:

A-(Infectious diseases)
- Typhoid fever
- Measles
- Scarlet fever
- Whooping cough
- Diphtheria
- Influenza
- Mumps
- Dysentery
- Acute poliomyelitis
- Meningococcal, meningitis
- Malaria
- Cholera nostra

B-
- Tuberculosis
- Pneumonia
- Broncho-pneumonia

C-(Circulatory diseases exclusive of acute cardiac diseases)
- Apoplexy
- Angina pectoris
- Other diseases of the heart (including endocarditis)
- Diseases of the arteries
- Other diseases of the circulatory system

D-(Acute cardiac diseases)
- Pericarditis
- Acute endocarditis and myocarditis

States included: Connecticut, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island, Vermont, and District of Columbia.

FIG. 14

curve for the ages 0–4 on the contrary has fallen sharply. Into the cause for this I need not enter. All the light dotted curves in the mid-region of the figure, one for each decade marked *A B D*, that is to say the curves representing infectious diseases *below* the age of 40 have likewise fallen. All the light solid lines marked *A B D*, one for each decade over the age of 40, have either fallen or remained horizontal, except for the age 90, and this one too has fallen in the last 10 years. That the death rate from heart disease below the age of 40 has fallen is apparent also in curve C_2, figures 3 and 4. In what decades the rates from infectious diseases have been affected, the movement of the total rate of which is seen in figures 3 and 4, is shown in figure 14 in which age specific curves are exhibited. It appears, on analysis, then that the rise in the death rate from heart disease has occurred exclusively after the age of 40, as the double lined curves, one for each decade marked *C*, show, and the rise has been the higher the higher the age. I am indebted to Miss Whittemore for the data in this and the next two curves.

If the increase in deaths from heart disease has resulted from transferring deaths due to defects in the arterial system or from some other indefinite heading to the cardiac group, a fall in the curve for diseases of the arteries should have taken place. That this is not the case is seen in these curves. And that the changes have taken place exclusively above the age of 40 is apparent from this further set (figs. 15 and 16).

A summary of the changes which have taken place in the past ten years is exhibited in figure 17. In fig. 17a are age specific curves for 1910 and 1920, both for males and females.[5] With the exception of a single half decade there is a fall in rate for each decade before the age of 60. The fall between the ages of 40 to 60 concerns the year 1910 only; in earlier years there is a conspicuous rise, as has already been shown. Above the age of 60 there is a uniform elevation of the 1920 curves above those of 1910.

In fig. 17b there is still another expression of the same phenomenon. Under the age of 60, the rate fell nine-hundredths, above the age of 60, it rose 17.12.

[5] For the data for these curves I am indebted to Dr. William H. Davis, Chief Statistician for Vital Statistics, Department of Commerce, Bureau of Census, Washington.

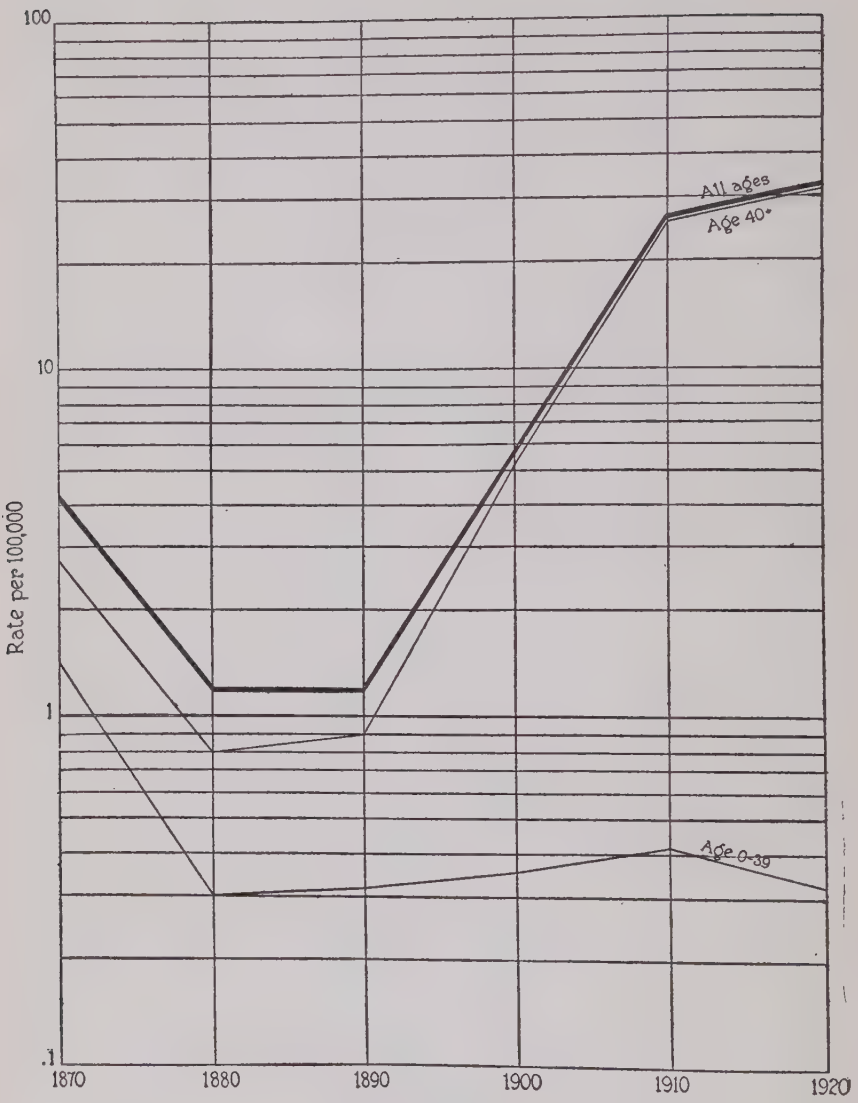

100
10
1
.1
Rate per 100,000
All ages
Age 40+
Age 0-39
1870
1880
1890
1900
1910
1920

FIG. 15

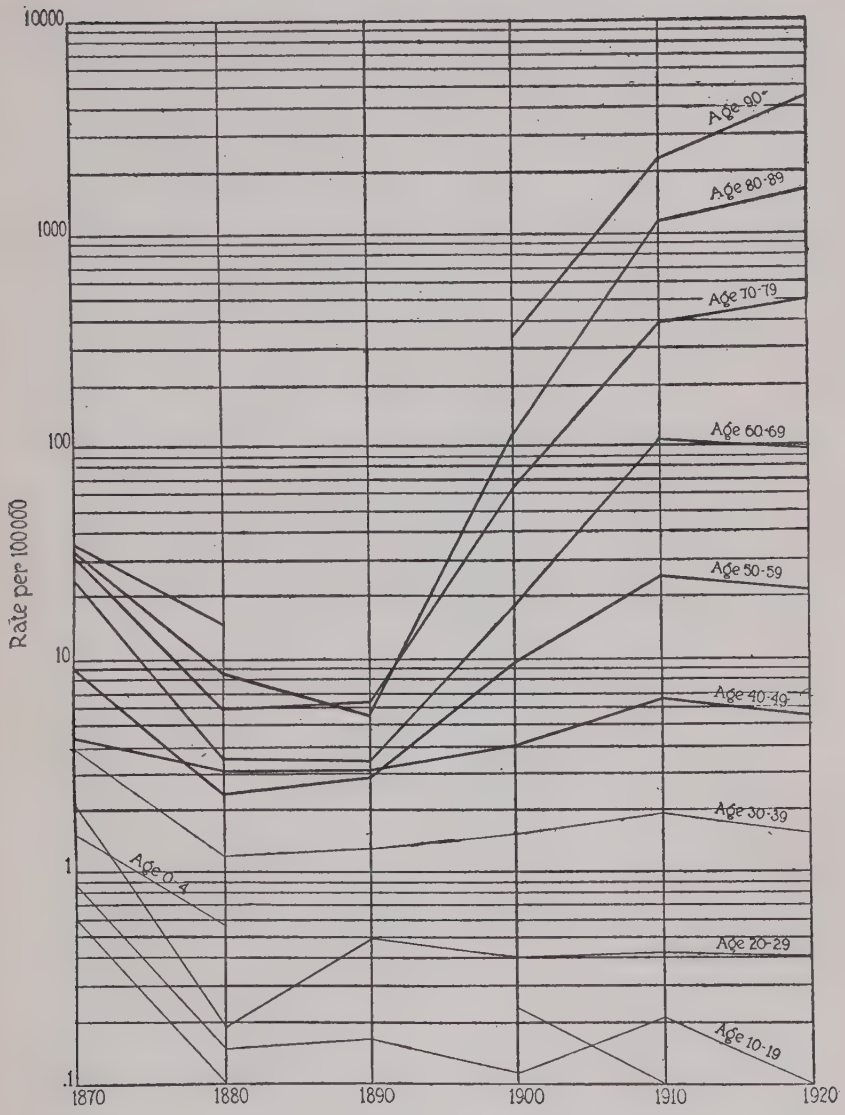

10000
1000
100
10
1
.1
Rate per 100000
1870
1880
1890
1900
1910
1920
Age 90-
Age 80-89
Age 70-79
Age 60-69
Age 50-59
Age 40-49
Age 30-39
Age 20-29
Age 10-19
Age 0-4

FIG. 16

Aside from the matter of treatment with drugs and by other means of which I have already spoken in connection with rheumatic fever and syphilis, the large number of persons who suffer from chronic heart disease places a charge on the public, to see to it that provision in appropriate institutions is made for their care. Public provision,

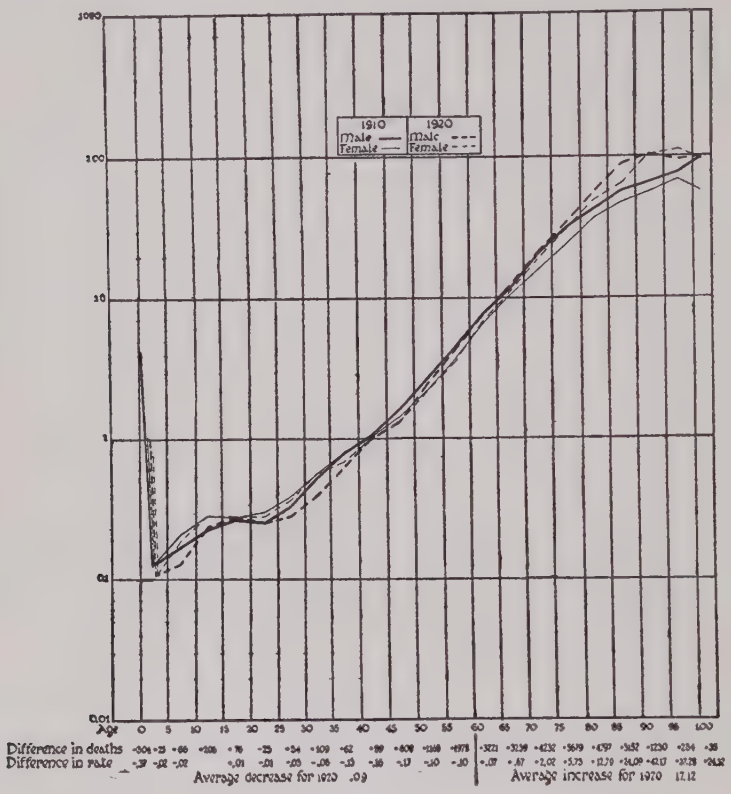


FIG. 17a

at least of two sorts, is requisite; the hospital, for what may be called the more acute or urgent phases of these diseases, or in the case of rheumatic fever, during the period of active infection in the febrile stage; and in the case of already established chronic disease, in the period when heart failure first appears. Later, for both types of cases, further provision is desirable when the course of disease is less

stormy, and while reconstitution on a new level of activity is being accomplished and a new way of life learned. What has come to be known as the convalescent home now supplies the second need.

Unfortunately I do not possess data covering the hospitals in the whole country. But in New York, I have figures which Emerson (67) has published. He found in 1920 or 1921, that in 10 of the larger New York hospitals 98,838 patients were admitted. Of these 4.6 per cent (4,522 cases) were cardiac. The average stay in hospital for each cardiac patient was 52.2 days. The per cent of all hospital days care

FIG. 17b

given to cardiac patients was 9.35. Notice that cardiac admissions were 4.6 per cent, whereas cardiac patients took 9.35 per cent of the hospitals' attention. The cost of a cardiac patient in the general hospitalization studies averaged $257.27. He suggested that a 100-bed convalescent cardiac hospital was needed. Dr. Emerson has in a letter explained to me the course of his reasoning. On account of its interest, I repeat his argument. Although heart patients represent only 4.58 per cent of all general hospital patients, they require, or at all events receive, twice as much care in proportion, to their numbers,

as other patients do, or 9.35 per cent of the total number of days given in the hospital study. Assuming that they were still in need of further bed care, probably an additional twenty to forty days per patient, a total stay of 40 to 80 days of hospitalization for each cardiac patient is estimated. Those of us who have had experience in hospitals know that not even this allowance suffices. They can, in point of fact, be better and more economically cared for elsewhere, as in convalescent homes. To find a basis for calculating the size of the home needed, Dr. Emerson proceeded as follows: The ten New York hospitals discharged 565 heart patients in one year. Assuming that they were still in need of care, say for additional 20 to 40 days per patient, a total stay of 40 to 80 days is obtained. A 100-bed hospital performing this service for 565 patients, the number of heart patients discharged in a year, could provide an average of 64.5 days per patient. Dr. Emerson goes on to say "Of course the correct way of determining the extent of the need for beds for chronic heart patients would be by studying the disposition of these patients on discharge from general hospitals and inquiring into the adequacy of home or other care provided."

There are meanwhile about New York 312 beds the year around available for heart patients in institutions, the total capacity of which is 910 beds; that it to say 34.2 per cent of the beds in eleven convalescent homes.

In the country at large, the convalescent home has likewise been developed. Whether the number of beds which is offered, suffices for the local requirements I do not know. There are 174 homes in 22 states, with a capacity of 10,201, about 60 per cent (6,076) being available all year, the remainder (4,125) for the summer only. They provide for cases of maternity, orthopedic defects, tuberculosis; a few only, exclusively for cases of heart diseases.

Meanwhile, with the decline in the death rate and in the morbidity from tuberculosis, the expectation should be realized, that of the large number of beds provided for tuberculosis, a certain fraction would be relinquished for heart disease. Mr. Drolet (69), the statistician of the New York Tuberculosis Association, in compiling the resources of the country concludes that this is not the case, but that on the contrary, the country is in arrears, 25,864 beds. He bases his com-

putation on the fact that there were 99,579 deaths from tuberculosis (1924) and only 73,715 beds. Presumably the deficit, he cites, leaves out of account those cases which find care at home, those which are provided for in institutions for the insane (5,500) and those for prisoners in State institutions (1,300). It might be pointed out that the figures Mr. Drolet cites are based on the rate of one institutional bed

TABLE 8

Summary of national directory of convalescent homes

STATES	HOMES	YEAR ROUND BEDS	SUMMER ONLY	TOTAL
Alabama	2	12	20	82
California	11	489	100	589
Connecticut	5	120	280	400
Georgia	1		50	50
Illinois	8	292		292
Kentucky	2		80	80
Louisiana	2	30	50	80
Massachusetts	24	476	228	704
Maryland	4	78	44	122
Michigan	1	135		135
Minnesota	3	187		187
Missouri	4	72	50	122
New Hampshire	1		10	10
New Jersey	23	875	668	1,543
New York	55	2,574	2,210	4,784
Ohio	4	160	40	200
Pennsylvania	18	479	75	554
Rhode Island	2	45	180	225
South Carolina	1			
Texas	1	24		24
Virginia	1	28		28
Washington, D. C	1		40	40
22 states	174	6,076	4,125	10,201

for each patient; but, he has pointed out the fact that this is an arbitrary arrangement, especially in view of the fact that "by actual count only twenty per cent of the deaths from tuberculosis in the United States take place in institutions." Nevertheless it has been found that the beds can be kept continuously filled. In 1925, patients in tuberculosis hospitals were found to stay on an average, close

to six months, namely, 174 days (69). But in general it appears that beds for heart disease cannot be acquired from beds fallen vacant from use for tuberculosis, even provided that hygienically, this could be accomplished. There are States, however, in which beds for tuberculosis are in excess of the apparent needs, as for instance in Arizona, Colorado, Connecticut, Massachusetts, and New York. In other states there is, however, a deficit, as for instance in Maryland, California, Ohio, and Pennsylvania. What arrangements it is possible to make in the interest of the transfer that has been suggested it might be important to investigate.

I trust enough has been said to show that, from practically every point of view, information is inadequate, so far unavoidably inadequate. Geographical distribution, etiology, age relation, infectivity, heritability, therapeutics—wherever the subject is touched there is uncertainty. Because of the general chaos in which the whole matter of heart disease lies, and because of the general lack of widespread information, there has been formed the Association to which I have already referred. In New York, where the pioneering has taken place, alongside of the heart association, there arose cardiac clinics which also formed an Association. There are now upwards of fifty of these clinics, well distributed through the greater city. Next, the Association and the clinics united and finally all were absorbed by the New York Tuberculosis and Health Association. Parallel with the New York City movement, a national association has been formed. The Heart Committee, as that part of the New York Tuberculosis Association is called which deals with heart disease, has as one of its committees a Committee on Research. This Committee has labored for several years with methods for collecting accurate and adequate data on the more general aspects of these diseases. It struggled for several years with devising forms (70) of reporting, and believes that the method which was developed is adequate to its purpose. The forms, which were produced, are used in the Bellevue Heart Clinic, the largest one in New York, and have served as the basis of a number of the statements I have been able to make in this report. If you were to look through the publications dealing with certain aspects of this subject, you would, I think, be surprised to learn how much information has flowed from this single source. If it is possible to study cases in

this manner at the Bellevue Clinic, it is, as we know already, possible elsewhere. Even with slender resources, this investigation has gone forward, with a very small permanent staff. With a grant recently acquired from the Commonwealth Fund, this study, after its period of trial, is to be expanded so as to include more clinics and to be more broadly based. Great effort has been made to safeguard at the source the value of the data. Agreement has been attained on nomenclature and classification, definition and diagnosis. Trained secretaries see to it that duplicate records from the various clinics are not brought together for collation until the record of each case has been edited and revised. The original records are the property of the clinics, and are retained by them for whatever use the clinics desire. Were the data entered, for which there is provision on the record forms, each phase of the whole problem which I have been discussing could receive adequate exposition, instead of the fragmentary information I have been able to lay before you. Accuracy of information can be attained only by this or by some other similar method. But the pursuit of the aim will lay considerable obligation on the public mindedness of those physicians who participate in this enterprise.

In the course of this exposition, I referred to the curves of Wyckoff and Lingg, in considering which there developed a danger encountered in drawing the morbidity curve, first on account of dilution among the younger, and second on account of paucity of cases among the older age groups. These are difficulties which can be avoided; there should be sought methods of compensating the defect, especially in the older age group. A utilization of the records in private practice can perhaps supply this need. That this method is practicable has already been demonstrated in New York, and that this example be imitated is distinctly desirable.

It has been the purpose of this report to place emphasis on the meaning for the public health of certain aspects of the heart diseases and of their occurrence. The most desirable plan for drawing attention to matters of this nature utilizes the statistical method; and this would also be the best method in a perfect world. Under the circumstances the use of the method has revealed how imperfect a world this is for just this purpose. But however imperfect the method, no other one is designed to present the facts. To eschew the method

because the results are defective and to fly to an extreme in which the classification of cases is neglected, but in which individual ones are described meticulously instead, begs rather than meets an important issue. Individual cases adequately and completely described remain without meaning from the point of view of probability until they are assembled in groups. But statements like this are elementary and would scarcely require mention were it not for the fact that, especially among the best observers the fact escapes notice that data as data remain sterile; not until they are brought into action in a larger world of relevance do they take on significance. That accumulations of facts, such as I have assembled, leave much to be desired is not surprising; it is on the contrary encouraging to reflect that a sound beginning has been made and that ways are being devised for improving the methods of acquiring and of tabulating knowledge of this sort.

It is important to review certain results which issue from this inquiry.

1. Attention should perhaps first be drawn to the fact that unlike tuberculosis, heart disease concerns an organ and not a simple etiological moment. Diseases of the heart result from a number of different injuries. In the case of the heart, three main groups can be distinguished: first, that associated with rheumatic fever; second, syphilis; and third, arteriosclerosis or, as I prefer to call it, the senescent process.

2. There can no longer be doubt of the fact that rheumatic fever affects persons in the first three decades predominantly; that syphilitic heart disease is rare before the third decade and is often delayed two decades more; and that if due allowance is made for the age of occurrence and for the duration of these two disease types, the preponderant number of deaths occurs after the age of 40.

3. It is borne out by study of the curves which relate infectious and heart diseases, that the two have moved in opposite directions. The curve which represents the former has been falling, while that of the latter has risen. But the relation is not quite simple, for neither curve travels a smooth course. It is, however, possible to notice that at certain points, changes in the direction of both curves have taken place. It is, furthermore, noticeable that there occurred a delay in

the increased rise of the curve from heart disease for a number of years after that of the infectious diseases began to fall. That this period is seventeen years may have a meaning, but it is not an obvious one and no insistence is placed upon it. That there should be a delay like this is easily comprehended; if individuals fail to die of infection, they will die in some other manner, and of affections which develop or are incident to life at later ages.

4. That the data which have been accumulated support this view seems clear, for the curves all show that the increased rate of death from the heart diseases involves persons over the age of 40. Under this age, the rates, as these curves show, have actually fallen. Additional confirmation of this view resides in the fact that the rate increases with each decade.

5. The inference to be drawn from these statements has an important bearing on the fears which have arisen on account of the obvious increase in the death rates due to the heart diseases. If, as the data show, the increase involves the older age groups only, the result is altogether gratifying. If men are, as the old adage has it, as old as their arteries, it becomes an important consideration to learn how long these may live. It they live their full span of years, death from old age and death from circulatory defect may prove to be the same thing. To die so would turn out to be the method of choice for the human organism; at all events, to realize it appears to be the direction which the course of events I have been describing, seems to be taking.

6. Environment, climate, latitude all appear to influence the incidence and course of rheumatic heart disease. But the data inspire no great confidence and suggest that the conditions under which they are collected be more precisely defined.

7. Experiences on the subject of treatment have been described. Apparently, from a remedial point of view, it is only in the rheumatic variety of heart disease that success can be anticipated from the use of methods designed to close the avenues of infection. The suggestion that patients be treated, as are the tuberculous, with continuous prolonged rest, deserves consideration. Too little is known now to justify the adoption of an opinion on this point.

It was my intention to show in this very incomplete summary that from the point of view of the public health, the problem of heart

disease is not simple as was that of tuberculosis, but manifold. It includes disability from infectious diseases, such as rheumatic fever and syphilis, and disability incident to the process of ageing. The effort to relieve rheumatic fever by removing areas of infection still wants prosecuting before a judgment on its value can be given. To prevent the onset of the disease is still impossible. Theoretically the situation in syphilis is more fortunate; practically the methods of prevention and treatment offer enormous difficulty. Nor has a final conclusion been reached on the value of treatment. There also more knowledge is wanted. The disabilities dependent solely on age, the major aspect of the problem, must elude approach on the side of etiology; to provide relief from distress must be the direction in which to expend effort.

If the infectious aspect of heart disease is, relatively speaking, small, smaller than is often thought, that is a happy discovery. But that the rate of so called chronic heart disease is high and is constantly mounting, that is a condition in which those may take satisfaction who believe increased length of life for more persons is one of the great blessings of men. The rise may be alarming, but it is not malign.

So many matters are, as I have tried to indicate, unclear that there must be general agreement that the idea which underlies the effort to accumulate information is sound and its prosecution desirable.

I should like to conclude these remarks with an expression of the pleasure I felt at receiving your invitation to make them as well as of the honor I know it to be, to be included among those who have had the opportunity to deliver De Lamar Lectures.

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SOME PIONEERS IN PARASITOLOGY[1]

GEORGE H. F. NUTTALL, F.R.S.

The pioneers of whom I shall speak have been selected from amongst other outstanding figures, partly because their portraits are available. I shall confine myself to the main work accomplished by each of those coming under consideration and must refer my readers to published biographies for more detailed information. The selected pioneers will be considered as far as possible in chronological order, in accordance with the dates of their birth. But three living pioneers are included, and the series begins with Kircher and Boyle, notable forerunners.

Athanasius Kircher (1601–1680) (portrait 1[2]), S. J., classical scholar, archaeologist, astrologist, mathematician, was born in Germany and died in Rome. Biologists will associate his name with the "experimentum mirabile" illustrated in his *Physiologia Kircherianum* (1680), where a fowl is shown lying prone with outstretched head upon a line drawn on flagstones.

In his treatise on plague, he states that he saw countless "minute worms" in the blood and pus from buboes of men suffering from the plague which raged in Italy in 1656. He used but a simple microscope, and doubtless merely saw red blood corpuscles and leucocytes or pus cells; nevertheless his teaching carried great weight in establishing the doctrine of *contagium animatum*. I, therefore, place him among the first pioneers. Kircher's views doubtless led

Robert Boyle (1627–1691) (portrait 2) to write in his essay on the *Pathological Part of Physic*, the following prophetic words, nigh on 250 years ago: . . . . "and let me add that he, that thoroughly understands the nature of ferments and fermentation, shall probably be much better able than he that ignores them to give a fair account

[1] December 20, 1926.

[2] Portrait of ca. 1665.

of divers phenomena of several diseases (as well as fevers and others) which will perhaps be never properly understood without an insight into the doctrine of fermentation."

The "pathological part of physic" had to await Pasteur to prove the correctness of Boyle's prophecy.

Francesco Redi (1626–1697) (portrait 3), a Tuscan nobleman, M.D. and Ph.D. of Pisa, a leader in science and letters, a poet and physician at the court of Florence. He was the first to experiment with snake venom, finding it most toxic when it enters the circulation and innocuous when taken by the mouth.

He exploded the wide-spread belief that maggots in meat and parasitic worms were spontaneously generated. He distinguished the sexes in intestinal worms, showed that they laid eggs and described the sexual organs of *Ascaris* of man. His treatise deals with the chief types of parasitic worms occurring in the intestine and various organs of many species of animals. He was one of the founders of parasitology, and his researches stimulated others to devote their attention to parasitic worms. In 1668 he published lists and figures of Pediculi and Acari parasitic on birds and mammals. He described ticks, and various insects concerned in myiasis. He recommended the use of red mercurial ointment in the treatment of itch.

Antony van Leeuwenhoek (1632–1723) (portrait 4), a distinguished figure in science, was a self-taught man. Apprenticed to a linen draper in his native town of Delft, he, at the age of 22 obtained a sinecure office which secured him ample leisure for the pursuit of scientific studies. He learned the art of lens-grinding and constructed some 400 microscopes, some of which were designed for special purposes. He never revealed the method he used for making his "best observation," saying that he "kept that for himself alone."

His communications began to reach the Royal Society, London, in 1673; some appeared in the Proceedings, others being still preserved there in MS. He was elected F.R.S. in 1680.

He is commonly referred to as the "Father of Microscopy," and he stands out as the first bacteriologist and first protozoologist. He saw many things that no human eye had previously discerned and

was remarkably objective in describing what he saw. Amid his many observations we may single out the following: He first saw parasitic protozoa (*Eimeria*) in 1674 and entozoic protozoa (*Giardia*) in 1681; in 1675–1680 he discovered bacteria, spirochaetes and beer yeast. He described bacteria found in the "materia alba" from between the teeth, in the intestine, and growing anaerobically in pepper infusion. He figured bacteria and parasitic protozoa.

He was apparently the first to attempt to raise *Pediculus humanus* experimentally, though he abandoned the effort after a trial upon himself. He studied the mechanism of feeding and the structure of the mouthparts in the louse, and figured nits.

His observation that the flea may be attacked by a mite gave rise later to the well-known lines by Swift (1667–1745):

> So, naturalists observe, a flea
> Has smaller fleas that on him prey;
> And these have smaller still to bite 'em,
> And so proceed ad infinitum.

Lazzaro Spallanzani (1729–1799) (portrait 5) was a great natural philosopher. He became Professor at Modena (1760-1757) where he wrote on Greek inscriptions, mathematics, physics, and worked on the regeneration of lost parts in animals and upon the circulation of the blood. He was elected F.R.S. about 1766. Proceeding to Pavia, he continued to work on many subjects, physiological and otherwise.

His classical researches on spontaneous generation, published in 1765, bore directly on microbic life. He showed that heated infusions, when unheated air was excluded, remain free from microörganisms and found that the latter multiply by fission.

Louis Pasteur (1822–1895) (portrait 6). Following upon his classical studies on molecular dyssymmetry, spontaneous generation and fermentation, upon which he threw a flood of light, that has remained undimned, the thought came to him that infective diseases might well be due to the action of microörganisms. He had attacked the problem of fermentation as a chemist, and had demonstrated that fermentation is due to the action of microörganisms, and, in agreement with Boyle's prophecy, proceeded to discover that certain

diseases are due to microörganisms. Pasteur had shown that alcoholic, acetic, lactic and butyric acid fermentations are due to specific organisms which he could cultivate and learned to recognize. He spoke of "maladies of wine" or of vinegar as due to injurious microbes. He was dominated by the thought that disease is probably due to similar causes.

He first attacked the subject of disease in silkworms (1865–1870) of which the more important, pébrine, now known to be due to a protozoal parasite belonging to the microsporidia, led to results which induced Pasteur to take up the greatest work of his life. Italian observers, prior to Pasteur, had observed minute bodies in infected eggs and caterpillars of silkworms. These bodies were found in infected female moths and Pasteur, by separating the eggs of uninfected moths from those that were infected, and using clean eggs only for propagation, afforded signal service to the silkworm industry of France which was threatened with extinction.

Following upon studies on beer (1871–1873) he attacked the subject of anthrax in the same year as Robert Koch, and then fowl cholera, and in 1880–1885 worked out the universally employed treatment for rabies. In 1881 he discovered that modifications in the virulence of bacteria could be induced and immunization practiced, notably against anthrax.

Pasteur's earlier work on fermentation and that on wound infection, together with his views regarding the causation of disease by microbic life, led Lister to introduce antiseptic methods into surgery, this being followed by the aseptic method now employed. In short, Pasteur revolutionized the methods employed in all industries dealing with fermentation, and revolutionized medicine and surgery. Before Pasteur, 5 per cent of women died of puerperal fever (at times 50 per cent died thereof in institutions); recent London figures record nearly 8,400 deliveries without a single case of puerperal fever.

The term "Pasteurization" has long been a household word. "Pasteur Institutes" dot the world. All honour to his memory. We may end this brief summary of his noble life's work with a brief sentence of his that should serve as a guide for those that follow: "Dans les champs de l'observation, le hazard ne favorize que les esprits préparées."

Rudolph Leuckart (1822–1898) (portrait 7), who worked in Göttingen, Giessen, and finally in Leipzig, as Professor of Zoology, distinguished himself especially in helminthology, his laboratory becoming a centre of active research. Many of his pupils became well-known parasitologists. He created the class Sporozoa among the Protozoa and worked on Linguatulidae and Pupipara. He did fundamental work upon the chief groups of helminths. The main work in tracing out the complete life-history of *Trichinella spiralis* was that of Leuckart and Zenker. His work on *Cucullanus* (1858), a nematode parasite of fish, served as a guide to his pupil Fedschenko in tracing the development of *Dracunculus medinensis* in *Cyclops*, in Turkestan (1869–1872).

Joseph Leidy (1823–1891) (portrait 8) was Professor of Anatomy and later Professor of Zoology and Comparative Anatomy at the University of Pennsylvania. His researches covered a very wide field. Here we can only refer to his exceptionally sound work in parasitology. He published 120 papers on helminths apart from those on protozoa. Of special interest to medical parasitologists was his discovery of immature *Trichinella spiralis* in the pig. This nematode had been found in man by Sir James Paget, as a student at Barts, and was named *Trichina spiralis* by Richard Owen (1835). Joseph Leidy discovered the parasite in American pork when cutting a cold ham sandwich, in 1847; the importance of the discovery lay in that it led Leuckart to make the important suggestion that man might become infected by eating raw pork.

Alfred Giard (1843–1908) (portrait 9), Professor at the Sorbonne, where he held the chair of "Evolution des êtres organisés," was the author of over 600 papers and founder of the Marine Zoological Station at Wimereux near Boulogne.

He distinguished himself in parasitology mainly through his classical researches on parasitic Crustacea and what he termed "parasitic castration" in animals and plants. Well known examples of parasitic castration are observable for instance in certain crabs where the parasitized male takes on the secondary sexual characters of the

female. Giard, moreover, discovered the *Orthonectidae*, a group of parasites that are intermediate between protozoa and metazoa.

Robert Koch (1843–1910) (portrait 10) took up the study of anthrax, when in practice at Wollstein in Polish Prussia, curtaining off a part of his consulting room for purposes of a laboratory. Through the work of the botanist Ferdinand Cohn he became convinced of the existence of different species of bacteria, and that means should be found to isolate them in pure culture, especially when engaged on researches in which possibly disease-producing bacteria were concerned. He worked out such methods, and in 1876 demonstrated the formation of resistant spores by the anthrax bacillus, both in cultures and in anthracic blood exposed to air. His researches supplied the first clear evidence of the causal relationship between a specific microorganism and an infective disease, his work being confirmed by that of Pasteur and others. He was the first to experiment with provedly pure cultures, to devise methods for staining bacteria, for demonstrating the flagella present in motile forms, taking photomicrographs of bacteria and improving the microscope for bacteriological work. His discovery of the method of isolating bacteria on solid gelatinized media, like his other methods, continues in use down to the present day with but slight modifications. He himself thought to the end of his life that the methods of bacteriological work devised by him represented his best contribution to science.

His discovery of spore formation in the anthrax bacillus confirmed a supposition previously expressed by Cohn who had observed spores in non-pathogenic bacilli which he had studied as a botanist. Obscurities in the etiology of anthrax were at once cleared up when the bacillus was found to be sporogenic.

Koch's discovery of *Bacillus tuberculosis* (1882) stands as a landmark in the history of medicine. The cholera vibrio was discovered by him in 1883, with the result that means had to be found for dealing with cholera and other water-borne diseases through the filtration of water, a subject in which Koch became much interested. In 1890, he discovered tuberculin, but this did not meet with the success for which he had hoped, and, after 1896, he spent much of his

time abroad, first in South Africa working on Rinderpest, then (1897) in Italy working on malaria. The results of his studies on malaria were mainly confirmatory of those of Ross, MacCallum and others. He was a strong advocate for the use of quinine in conjunction with malaria prophylaxis, and devised preventive measures that bore good fruit in German East Africa and New Guinea. In 1902 he did valuable work on East Coast Fever in South Africa, discovering what are still called "Koch's bodies," which constitute a phase in the developmental cycle of the parasite and are of use in diagnosis. In 1906 he worked on sleeping sickness, used atoxyl for the first time in the treatment of the disease and devised methods of clearing the foreshore of lakes as a measure against *Glossina palpalis*, the vector of the sleeping sickness trypanosome.

Mankind will remain indebted to Robert Koch for all time. By his researches and those of the School which he founded he did a truly great work for humanity.

Patrick Manson (1844–1922) (portrait 11, taken in 1911), a Scotsman, born a year after Koch, after making his M.D. in Aberdeen, proceeded to the Far East, sojourning in Formosa for five years and in China, at Amoy and Hongkong, for eighteen years. He practiced medicine until a few years before his death. His main contribution to parasitology consisted in the discovery, in 1877, of the phenomenon of "filarial periodicity," namely the periodic increase in the number of microfilariae present in the blood circulation of man, which led him to suspect that mosquitoes might serve as hosts of *Filaria bancrofti*. He tested this experimentally, and observed the partial development of the microfilaria, as described in his papers dating from 1878 to 1884. It should be remembered that he made his experiments while busily engaged in practice. He found that but one out of four species of mosquito served as hosts for the worm, an observation which proved suggestive in connection with Ross's subsequent work on malaria. In 1890 he returned to London where he resided until his death. In 1894 he formulated a theory—he not merely conjectured as others had done before him—that malaria was a mosquito-borne disease, laying special stress upon the phenomenon of "exflagellation" exhibited by the parasite in extravascular blood

as pointing distinctly to its further development in a blood-sucking insect.

He convinced Ronald Ross that he should work out the problem in India, giving him, as Ross himself wrote in 1900 "a chain of reasoning from which it was impossible to escape. . . . . I have no hesitation in saying that it was Manson's theory, and no other, which actually solved the problem; and to be frank, I am equally certain that but for Manson's theory the problem would have remained unsolved at the present day."

Manson's name remains associated with that of a number of parasites (*Schistosoma*, *Sparganum*, *Oxyspirura*, etc.), with the discovery of which he was concerned. In 1899, Schools of Tropical Medicine were established in Liverpool and London owing to the impulse emanating from Manson. Raphael Blanchard, on the occasion of the International Congress of Medicine in London in 1913, fitly styled him "The Father of Tropical Medicine."

Alphonse Laveran (1845–1922) (portrait 12, taken in 1901), son of a military surgeon, followed his father's profession, proceeding to Algeria in 1878. He took up the study of malaria with the aid of a microscope and, in 1880, while at the Military Hospital of Constantine, he made his great discovery of the malaria parasite which he described in publications dating from 1880 onwards. He retired from military service in 1896 and joined the Institut Pasteur, there devoting himself to protozoology, publishing numerous contributions dealing more especially with malaria, trypanosomiasis and leishmaniasis. He worked indefatigably to the end.

The significance of his discovery of the malaria parasite was only slowly appreciated, but with time his observations were confirmed everywhere. The presence of the parasite in the blood became a matter of prime importance in diagnosis. In 1884 he suspected that mosquitoes convey malaria, but he did not contribute to the elucidation of this aspect of the problem. His discovery came to be appreciated throughout the world and he was the recipient of many honours.

Elias Metchnikoff (1845–1916) (portrait 13), the famed zoologist, began his researches with the investigation of marine animals; his

first contribution to parasitology related to *Ascaris nigrovenosa* of the frog (1865). He was the founder of the well known phagocyte theory. In 1884 he described the phenomenon of phagocytosis of a yeast-like parasite in the fresh water flea, *Daphnia*, and henceforward devoted years of work to the study of phagocytosis and immunity. Abandoning Russia, he established himself at the Pasteur Institute in 1888. He studied the problems of old age and the whitening of hair and their causes as well as dietetics in relation to the intestinal flora. Alone and with Roux, he did most important experimental work on syphilis in apes and monkeys which, from a practical standpoint afforded means for the protection of those that may have been in contact with infection. His ashes repose in an urn in the library of the Institut Pasteur.

Walter Reed (1851–1902 (portrait 14). The work of Reed is known throughout the world—all of us who knew him will ever think of him with pride. He and his companions forged the weapons wherewith to conquer a disease that levied a heavy toll on mankind for centuries.

Professor W. H. Welch, in a letter to the Secretary of War of the United States, truly stated of Reed's researches on Yellow Fever, that they formed one of "the most valuable contributions to medicine and public hygiene which have ever been made in this country with the exception of anaesthesia. They have led and will lead to the saving of thousands of lives."

The United States Army Commission on Yellow Fever, 1900, consisted, as most of you know, of Reed, Carroll, Agramonte and Lazear, whose names will go down linked together in the records of medical discovery, but the name of Reed who was President of the Commission, will stand foremost, for, as General Leonard Wood once stated, Reed's was the "originating, directing, and controlling mind."

It will always be a source of gratification to me that Reed responded to my request to write an account of the work of the Commission for publication in the Journal of Hygiene (vol. II, 1902), especially since the summary which he gave was generally recognized as affording the best history of the work he had accomplished.

William Crawford Gorgas (1854–1920) (portrait 15[3]) can scarcely be omitted from this list for, although he was not a parasitologist, his name will ever be closely associated with the subject of yellow fever. He carried out the recommendations of the Commission, and developed and applied sanitary measures which led to the stamping out of yellow fever in Havana for the first time in history as the result of operations which were instituted in February, 1901. Furthermore, the measures devised by Gorgas rendered it possible to build the Panama Canal. The work on the Canal began in 1904, and within two years yellow fever was eradicated and malaria almost wiped out. His splendid achievement obtained universal recognition.

He was taken ill when on his way to study the supposed yellow fever of West Africa. Whilst he lay at the Military Hospital in London he was visited by His Majesty King George on June 8, 1920, receiving from the King's hands the insignia of Knight Commander of St. Michael and St. George. He died on July 4, and was accorded a full military funeral with a service at St. Paul's, whilst guns were fired in Hyde Park. This was the highest honour that England could pay to the "great medical administrator who died in our midst."

Friedrich Löffler (1852–1915) (portrait 16, taken in 1907), co-discoverer of the glanders bacillus with Schütz (1882) and the causative agent of swine erysipelas. Löffler was the first to show that animals recovering from a bacterial disease (mouse septicaemia) are immune against reinfection. He was the first to isolate the diphtheria bacillus in pure culture and give conclusive proof that the organism previously seen by Klebs is the cause of diphtheria. With Frosch and Uhlenhuth (1897–1905) he showed that foot and mouth disease is due to a filterable virus, this being the first instance in which an ultramicroscopic microörganism was found to cause a disease in animals. Löffler's work was sound throughout and has stood the test of time.

Emil von Behring (1854–1917) (portrait 17, taken ca. 1907). In 1888–1890, Roux and Yersin discovered that cultures of the diphtheria

[3] Portrait signed and dated 9.II.1920, which he sent to me.

bacillus contained a toxin that was responsible for the pathogenic effect of the bacillus, while Faber and Kitasato, in 1890, found that the tetanus bacillus likewise produced a toxin. In 1890, Behring and Carl Fraenkel discovered simultaneously that they could render animals immune against diphtheria toxin, and Behring ascertained that the serum of immune animals possesses antitoxic properties. This was soon followed by the announcement by Behring and Kitasato that tetanus antitoxin was curative when used in the early stages of infection in experimental animals.

The discovery of serum therapy by Behring is one of the greatest achievements recorded in the history of medicine.

At this juncture Ehrlich appeared on the scene and perfected the methods of toxin and antitoxin production and standardization, so that in 1894 the diphtheria antitoxin could be issued for use in general practice. These results were confirmed by Roux in the same year, while Nocard (1894–1897) demonstrated the great value of tetanus antitoxin in the prevention of tetanus in horses. While sufficiently convincing, although the treatment was only applied to horses by Nocard, and to some extent in practice by physicans, it was in the Great War that the value of tetanus antitoxin in the treatment of man was demonstrated in a manner that carried full conviction to medical men.

Paul Ehrlich (1854–1915) (portrait 18, taken ca. 1902) began his researches with studies on the histology of the blood. In 1877 he was struck by the existence of a chemical affinity between certain organs and chemical poisons, as instanced in the case of lead, and this led him to formulate his theory of selective anchoring between certain tissue cells and particular poisons or dyes. He induced immunity to vegetable poisons (ricin, abrin, rubin), and, following Behring's work on toxin and antitoxin, discovered the present day methods of standardizing toxins and antitoxins. He distinguished active from passive immunity. His work at Steglitz, begun in 1896, led to his evolving his famous side-chain theory which greatly stimulated research on immunity.

Beginning with the year 1899, when established at Frankfurt, he made important researches on haemolysins, cancer (carcinoma and

sarcoma), and chemotherapy. An interesting discovery related to the acquired resistance of trypanosomes to arsenical drugs. He discovered atoxyl and salvarsan and modifications of these that served as remedies in the cure of trypanosomiasis and syphilis, thereby rendering an enormous service to mankind.

David Bruce (portrait 19, taken in 1921), who was born in 1855 in Melbourne, Australia, served for many years in the Royal Army Medical Corps. While stationed at Malta (1887) he discovered the *Micrococcus melitensis*[4] to be the cause of Undulant or Mediterranean Fever, and in 1904–1906 went as Director of a Royal Society Commission to prosecute further studies upon the disease in Malta. The discoveries made by Bruce's Commission were of great practical importance, it being found that the Maltese goats were frequently infected with *M. melitensis*, and that they eliminated the microorganism in their urine and milk. This led to measures being taken which proved effective in controlling the disease.

In 1895, Bruce went to Zululand to study Tse-tse Fly Disease whose ravages had long been known among cattle, horses and dogs. Livingstone had attributed the fatal effects of this disease to the influence of a venom injected into animals by the fly. Bruce discovered trypanosomes in the blood of the affected animals, and demonstrated by experiment that the disease, known to the natives as "Nagana," is conveyed by *Glossina*. It was natural, therefore, that he went to Úganda in 1903, and again in 1908–1910, as Director of the Royal Society Commission to investigate Sleeping Sickness, being accompanied by his wife who, in an unobtrusive way, has afforded much efficient aid in her husband's researches. The work of the Commission was excellently carried out with the aid of an efficient staff.

Battista Grassi (1854–1925) (portrait 20[5]), the renowned zoologist, was born at Rovellasca, Como, took his M.D. at Pavia and became Professor of Zoology at Catania (1883) and afterwards Professor of Comparative Anatomy at Rome (1895), a post which he held until

[4] Termed *Brucella melitensis* of recent years.

[5] Portrait taken in 1913 by Prof. N. Pavlóvsky at Petrograd.

his death. He did pioneer work in connection with many different groups of parasites and published many papers, some of which deal with problems outside the domain of parasitology. He was an enthusiastic and indefatigable worker and a ruthless controversialist. To solve the riddle of the life-cycle of various parasites, vermes and protozoa, he did not hesitate to experiment upon himself. From his knowledge of *Ancylostoma caninum* he was the first to suggest that human faeces should be examined for ova in cases of suspected ankylostomiasis in man. He and Parona ingested *Ancylostoma duodenale* eggs and found them innocuous, but they infected themselves when they ingested the larvae. This was at the time when the parasite was recognized by Perroncito as the cause of anaemia among the workmen at the St. Gothard tunnel in 1880. Some of his best work on vermes relates to their mode of transmission by intermediate hosts. Of outstanding merit were his researches on avian and human malaria. We need not enter here upon the subject of the priority feud between Ross and Grassi in relation to discoveries on malaria. There is much to be said on both sides. Grassi's last word on the subject appeared in my journal *Parasitology*, December, 1924, and Grassi died on May 4, 1925. Ross has expressed his views with extraordinary vigor in his Memoirs (1923).

Ronald Ross (portrait 21, taken ca. 1900), who was born in 1857, is renowned for his researches upon the life-history of the malaria parasites. Untrained in zoology, and working with simple methods under unfavorable circumstances, inspired by a theory profounded by Manson, he observed the first stages in the development of the human parasites in Indian *Anopheles*, and worked out the life-cycle of *Proteosoma* of sparrows, thereby pointing out clearly the way in which malaria is communicated to man. In 1895 he saw the process of "exflagellation" take place in the mosquito; in 1897–1898 he observed crescent-derived pigment-bearing parasites in the gut wall of *Anopheles*, and followed out the complete cycle of development of *Proteosoma*.

The subject that he most affects is mathematics and he has written poetry.

Raphael Blanchard (1857–1919), (portrait 22, taken ca. 1913) started the first courses in parasitology in France at the École de Médecine, Paris. In 1889, with Milne-Edwards, he organized the International Congresses of Zoology. He took an active part in establishing the International Rules of Zoölogical Nomenclature, since so widely adopted. In 1894 he became Professor of Medical Zoology, the title of his chair being changed to that of Parasitology at his own request in 1903. A voluminous writer on many subjects, he founded the Archives de Parasitologie in 1898, which died with him, but have been replaced by a journal started by his able successor Professor E. Brumpt.

Blanchard was an indefatigable worker, a good organizer and orator, altogether a highly gifted and versatile man, whose shining presence at international meetings has left an indelible impression on those who knew him. He did much to further the study of parasitology and tropical medicine both in France and abroad.

Theobald Smith (portrait 23, taken in 1909), who was born in 1859, held the post of Director of the Pathologcal Laboratory in the Bureau of Animal Industry, U. S. Department of Agriculture, during the years 1884–1895, and Professor of Comparative Pathology at Harvard in 1896–1915, after which he became Director of the Department of Animal Pathology at the Rockefeller Institute, New York.

The idea that cattle-ticks stood in causal relationship to Texas fever, prevailed among cattle owners in the United States; therefore, Cooper Curtice (1891) studied the biology of *Boophilus annulatus* in view of the suspicion that rested upon this species. In 1893, Theobald Smith and F. L. Kilborne published the results of their researches, conducted during the years 1889–1892, under the title "Investigations into the Nature, Causation and Prevention of Texas or Southern Cattle Fever," proving by classical experiments that the redoubtable disease Texas Fever, Redwater, or Piroplasmosis, as it is variously called, is due to a protozoan parasite, *Piroplasma bigeminum* which is transmitted by *Boophilus*.

Theobald Smith's name will ever be associated with this discovery, which Professor W. H. Welch referred to at the time as a "romance in pathology." Theobald Smith's demonstration proved of out-

standing importance since it afforded the first conclusive evidence that an arthropod may serve as a vector of a protozoal disease.

Arthur Looss (1861–1923) (portrait 24), a pupil of Leuckart at Leipzig, held the chair of Biology and Parasitology at the Cairo School of Medicine from 1896 to 1914, when he was expelled for sufficiently valid reasons. He was an enthusiastic, most careful and painstaking research worker and an admirable draughtsman, as his publications testify. He worked chiefly on Trematodes and Nematodes. His most striking discoveries related to *Ancylostoma*—the penetration of *A. duodenale* larvae through the skin, first observed on himself (1898, 1901), and the similar entry of *A. caninum* into the dog. He followed the migration of the larval worm through the dog's skin, to the lungs and thence into the trachea and into the host's intestine (1904). This discovery was of great practical importance since it pointed the way to the effective prophylaxis of one of the worst scourges of mankind in hot countries.

The foregoing survey fails to mention Swammerdam (1637–1685) because no portrait of this distinguished man of science has come down to us. Leading bacteriologists have been included because, broadly interpreted, bacteriology belongs to parasitology. The selection of the pioneers may seem somewhat arbitrary, but looking back we see how much the work of these pioneers was interrelated.

The doctrine of contagium animatum, advanced by Kircher, may be taken as the starting point of parasitology.

The scientific study of minute vegetable and animal organisms began with Leeuwenhoek.

The work on spontaneous generation, begun by Redi and Spallanzani, culminated in that of Pasteur who finally disposed of the doctrine.

Parasitic insects and helminths were known to the ancients. The study of their life-history, begun by Redi, Spallanzani, Leeuwenhoek and Swammerdam, was developed chiefly in the nineteenth century by numerous observers.

The parasitic protozoa were first seen by Leeuwenhoek but the study of their life-cycle belongs chiefly to recent decades. The dis-

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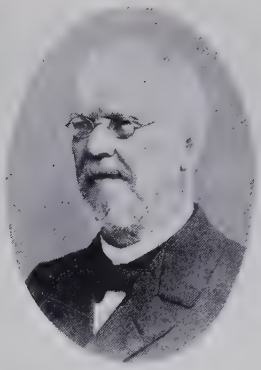

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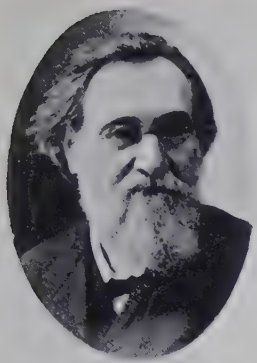

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covery of the malaria parasites of man by Laveran and that of the mode of conveyance of avian and human malaria by Ross, Grassi, and others, greatly stimulated research on parasitic protozoa, especially in relation to disease in man and higher animals. The same may be said of the work of Smith and Kilborne relating to the tick conveyance of Texas fever and that of Bruce and Nagana and the Tse-tse fly.

A great impetus to research emanated likewise from the discovery of the mode of transmission of yellow fever by Reed and his collaborators.

Löffler was the first to discover that ultramicroscopic organisms may cause disease, thereby opening a fresh field of research.

The study of immunity, begun by Pasteur, was greatly furthered by Metchnikoff, Behring, Ehrlich and many others—the subject concerns every branch of parasitology.

Looking back upon the pioneers we have considered, the names of Pasteur, Koch, Metchnikoff and Ehrlich stand out preëminently, not only for the discoveries they made, but for the schools they founded and the great stimulus they gave to scientific research.

LIST OF PORTRAITS

1. Kircher (1601–1680)
2. Boyle (1627–1691)
3. Redi (1626–1697)
4. Leeuwenhoek (1632–1723)
5. Spallanzani (1729–1799
6. Pasteur (1822–1895)
7. Leuckart (1822–1898)
8. Leidy (1823–1891)
9. Giard (1843–1908)
10. Koch (1843–1910)
11. Manson (1844–1920)
12. Laveran (1845–1922)
13. Metchnikoff (1845–1916)
14. Reed (1851–1902)
15. Gorgas (1854–1920)
16. Löffler (1852–1915)
17. Behring (1854–1917)
18. Ehrlich (1854–1915)
19. Bruce (1855–)
20. Grassi (1855–1925)
21. Ross (1857–)
22. Blanchard (1857–1919)
23. Theobald Smith (1859–)
24. Looss (1861–1923)

Representing the following countries

Germany	7
France	4
United States of America	4
England	4
Italy	3
Russia	1
Holland	1
	24

HISTORY OF TULARAEMIA[1]

EDWARD FRANCIS

Surgeon, United States Public Health Service, Washington, D. C.

The discovery of a new disease is an important milestone in medical history. In the history of human medicine there is only one instance in which American investigators alone have discovered a disease of man, isolating its causative agent, determining its sources of infection and its modes of transmission to man, describing its symptomatology and pathology, and otherwise elucidating the many essential problems connected with the complete knowledge of a disease. That is the story of tularaemia, and, carrying the thought a bit farther we find the words of Victor C. Vaughan (1): "Tularaemia, a disease discovered by the United States Public Health Service."

SYNONYMS

Bacteriologists, serologists, practicing physicians, ophthalmologists and entomologists have shared in this discovery, and for the most part each made his first observation while in ignorance of the work of the others. Owing to the varied circumstances under which each observer first encountered the disease in widely separated States, a variety of names or synonyms sprang up, and we find: plague-like disease of rodents, deer-fly fever, conjunctivitis tularensis, rabbit fever, glandular type of tick fever, tularaemia, and Ohara's disease.

PLAGUE-LIKE DISEASE OF RODENTS

McCoy (2) in 1911 contributed the first scientific knowledge of the disease by his discovery of what he called "plague-like disease of rodents" prevalent among the California ground squirrels, but first observed in squirrels which he received from Tulare County, California. McCoy and Chapin (3, 4), in 1912, discovered the causative organism of the disease in the California ground squirrel and named

[1] January 10, 1927

it *Bacterium tularense* after Tulare County. McCoy and Chapin (3, 4), in 1912, reported complement fixation and agglutination of *Bacterium tularense* by the serum of Chapin and of a laboratory attendant, both of whom were extensively engaged in handling or dissecting infected rodents in the San Francisco laboratory and who were the first cases of laboratory infection of man of which there have now been twenty.

Laboratory infection of man: The Public Health Service records show that ninety-four days after beginning work with tularaemia animals in the San Francisco laboratory, Dr. Chapin was granted twenty-eight days' leave of absence, beginning March 1, 1911, on account of sickness, the nature of which could not be diagnosed. The illness was accompanied by fever, was unaccompanied by glandular enlargement or other local lesion, and incapacitated this officer for all duty for twenty-eight days. No absence from duty on the part of the laboratory attendant can now be recalled by Dr. Chapin. Shortly after returning to duty Dr. Chapin discovered the positive findings in his own serum and in the serum of his attendant. In the light of present knowledge it is certain that what to McCoy and Chapin was a puzzling circumstance (the presence of *anti-tularense* agglutinins and complement fixing bodies in the serums of two laboratory workers) was the proof of two unrecognized human cases of tularaemia, identified *serologically*.

Ground squirrels of the species *Citellus beecheyi*[2] Richardson, were the rodents in which McCoy discovered the disease in the first part of 1910 (5). His original description was based on a study of 46 naturally infected ground squirrels which had been shot in nine counties of California, lying between Los Angeles on the south and the Sacramento River on the north.

McCoy (2, 4) found that the squirrel flea, *Ceratophyllus acutus* was a very feeble transmitter of the infection from ground squirrel to ground squirrel in the laboratory, and that it failed to transmit the infection from guinea pig to guinea pig.

Manner of discovering the disease: McCoy was the Director of the United States Public Health Service plague laboratory at San Francisco

[2] Miller (1924), in his list of North American recent mammals, classifies this as a subspecies, *Otospermophilus grammurus beecheyi*.

from March, 1908, to November, 1911, charged with the examination of rats and ground squirrels for evidence of plague. These rodents were trapped and shot in all parts of the state and shipped to his laboratory for demonstration of plague. His routine procedure comprised examination of lymph nodes, liver, spleen and lungs of these wild rodents for gross lesions of plague, inoculation of suspected lesions into guinea pigs, and in case of death of guinea pigs with typical lesions of plague, demonstration of *B. pestis* in cover glass preparations and cultivation of *B. pestis* from guinea pigs on plain agar and plain bouillon. Many ground squirrels conformed to all these requirements for the demonstration of plague, but many conformed to all except the last two, i.e., no microörganism was visible in cover glass preparations of guinea pig lesions, and no growth occurred on plain agar and plain bouillon which had been inoculated with guinea pig lesions. McCoy concluded that the latter squirrels comprised a group which was suffering from a new disease, which in its gross manifestations in guinea pigs was almost indistinguishably plague-like and which he designated "plague-like disease of rodents." The new infection was discovered in districts and even on ranches which had furnished plague squirrels and also in districts in which no plague was demonstrated.

From 1910 until the present time a few instances of infection with *Bacterium tularense* have been encountered each year among ground squirrels shot in various parts of California and sent to the United States Public Health Service laboratory at San Francisco for examination as part of the general antiplague campaign. The number of squirrels found infected with tularaemia has remained small, probably because the squirrel flea is a feeble transmitter.

Wild rabbits (6) were shot in various counties of the state and examined under McCoy's direction in the plague laboratory for evidence of plague and tularaemia with entirely negative results. In 1909, the number examined was 88; in 1910, 658; in 1911, 2654, and in 1912, none.

On first thought it seems queer that with a ground squirrel reservoir of tularaemia in California, no human case, other than three laboratory infections of the disease, has ever been reported from that state during the time that human cases have been recognized in 36 other

states, the District of Columbia and Japan. The explanation seems to be found in the low level maintained by the infection in ground squirrels and the absence of infection in wild rabbits. The situation adds emphasis to the necessity of a rabbit reservoir of infection in order to give rise to human cases in nature.

One cannot think of the completeness of our knowledge of tularaemia and the abruptness with which McCoy's "plague-like disease of rodents" has become a national and international disease without stopping to admire the tenacity with which McCoy and Chapin pursued their subject and better still, the final scientific touch that characterized their work. How easy it would have been for McCoy to take the view that, at best, they were dealing with only a comparatively rare infection of ground squirrels, and that it would be a waste of time to pursue such an unimportant matter.

DEER-FLY FEVER

In Utah a disease of man was for several years popularly known as "deer-fly fever" owing to the belief that the infection was due to the bite of the blood-sucking fly *Chrysops discalis*, commonly found on horses. This belief found expression in a paper read before the Utah State Medical Association, Salt Lake City, October 3, 1910, by Dr. R. A. Pearse (7), of Brigham City, Utah. Pearse's cases constitute the first reported human cases of tularaemia differentiated *clinically*.

Pearse's report deserves the following summarized description: He gives the histories of six cases which he saw in 1908, one of which died on the fifteenth day; he refers to three which he saw in 1910, and mentions several, observed by other physicians of his locality. Pearse's cases occurred in the month of August and followed the bites of a horse fly on the exposed parts of the body (neck, ear, cheek, wrist, ankle and hand). After an incubation of from two to five days, the glands that drained the bitten area became markedly swollen and went on to suppuration in about half of the cases. In all the cases the site of the fly bite progressed from a red infiltration to complete breaking down of the tissues and sloughing, resulting in a punched-out circular ulcer, about $\frac{1}{4}$ inch in diameter and $\frac{1}{8}$ inch in depth. Most of the patients had severe chills during the incubation period. The temperatures ranged from 98° to 104°F. The duration of the

disease was from one to four weeks, and the severity varied "from slight malaise to death."

I have received personal communications from a number of physicians; to these I shall refer briefly. Dr. T. B. Beatty, state health commissioner of Utah, informed me of a fly-bitten patient whom he had in 1914 near Tremonton, Utah. Dr. R. B. Stevens of Fillmore, Utah, saw 8 cases in 1919. Dr. Homer D. Junkin of Idaho Falls, Idaho, wrote that 14 cases were reported to the Idaho Falls Medical Society in October, 1921, of which he had 5. Dr. Charles Stuart Moody, of Menan, Idaho, reported 3 cases in 1923. Dr. E. Dietsche of Klamath Falls, Oregon, observed 2 fly-bitten cases in 1925.

CONJUNCTIVITIS TULARENSIS

Vail (8), Sattler (9) and Lamb (10), three ophthalmic surgeons of Cincinnati, Ohio, each reported a case of "conjunctivitis tularensis" in 1914, 1915 and 1917 respectively, in persons who had dressed rabbits and in whom the seat of primary localization was the conjunctival sac. The bacteriologic diagnosis of these 3 eye cases was made by Wherry and Lamb (11) who isolated *Bacterium tularense* on a culture medium from guinea pigs into which eye scrapings had been injected. Vail's case is the first human case of tularaemia on record to be diagnosed *bacteriologically*. There have now been reported 25 cases of primary infection of the eye.

Wherry and Lamb (12, 13) also isolated the organism from two wild cotton tail rabbits found dead and collected in southern Indiana near the residence of Sattler's patient. Their isolation of *Bacterium tularense* from wild rabbits was the first bacteriological proof of the rabbit reservoir of infection. It is of interest that Dr. W. B. Wherry was an Acting Assistant Surgeon of the United States Public Health Service from 1907 to 1909, stationed in San Francisco and Oakland, California, and engaged in the laboratory examination of rats and ground squirrels for plague as part of the federal and city plague-suppressive measures.

Martin (14, 15), an ophthalmologist of Arizona, had already sought advice in 1907 regarding a symptom-complex new to him which he had observed in five human cases, three of which showed primary localization in the eye and all of which had derived their infection from skinning and dressing "jack" rabbits.

The following letter, brown with age, dated September 19, 1907, was found in 1925 in a forgotten file by Dr. Frederick G. Novy of Ann Arbor, Michigan, who marked it "tularaemia" and sent it to me. In the light of present knowledge, it constitutes the very first description of cases of tularaemia, of which three were eye infections.

Phoenix, Territory of Arizona,
September 19, 1907.

Dr. Frederick G. Novy,
Ann Arbor, Michigan.

Dear Doctor:

There have been during the summer several individuals in this locality who have suffered from an infection as a result of skinning and dressing wild rabbits. They were of the so-called "jack" variety. Three of these persons have had their primary lesions in or about the eye. Small abscesses formed in the lids and on the bulbar conjunctiva as well. In one case the cornea was involved, the preauricular gland being involved, as well as the anterior cervical and the submaxillary. At the onset there were chills, profuse sweating and an elevation of temperature of from 2 to 5 degrees, with rapid pulse, lasting several days. The glands suppurated and all were evacuated. In one case a nodular condition of the lids still remains. There were no deaths; in fact, the illness was not profound. In one instance the infection took place in the foot, and others in the hands, etc., the adjacent lymphatics, of course, being involved.

Yours very truly,
Ancil Martin, M.D.

One of Dr. Martin's cases of 1907 still showed *anti-tularense* agglutinins in 1925.

TULARAEMIA

Francis (16) was detailed to Delta, Utah, in July, 1919, in response to a request from Dr. T. B. Beatty, State Health Commissioner of Utah to the Surgeon General of the United States Public Health Service to investigate "deer-fly fever." He established a field laboratory and very soon recognized the identity of the Utah human disease "deer-fly fever" and the California ground squirrel disease "plague-like disease of rodents" and named the disease tularaemia

(17) on account of the presence in the blood of the causative organism *Bacterium tularense*.

He furnished proof of this identity by isolating *Bacterium tularense* from 7 fly-bitten human cases, from 17 wild jack rabbits shot or found dead, and from 1 ground squirrel; by demonstrating *anti-tularense* agglutinins in his own blood and in the blood of Mayne, both of whom had contracted the disease in the field laboratory; and by transmitting the infection among laboratory animals by deerflies, *Chrysops discalis* (18).

The derivation of the words tularense and tularaemia is of interest. McCoy and Chapin named the organism *Bacterium tularense* after Tulare County, California, whence came principally the ground squirrels in which McCoy discovered "plague-like disease of rodents." The region of Tulare County was in previous years called Tulares by the Spaniards, because that area was covered by extensive marshy beds of reed called tule (Aztec), meaning a variety of large bulrush.

Tuleberg was formerly the name of Stockton, California, in the early days when Stockton was a mere settlement in the flat tule area of the San Joaquin River. To-day, in San Francisco, an old-timer refers to fogs in the direction of the San Joaquin river and Sacramento river as tule fogs. In Mexico the tule is used for weaving baskets and a cheap quality of bottoms for chairs which are known as tule chairs. The San Blas Indians of Panama recently sent to the United States Government at Washington a petition, approved by the "Tule National Congress" for a protectorate over Tule.

Tularaemia is, therefore, a hybrid word of Aztec and Greek origin. To a Greek purist the name is barbarous and shocking, but to a poor market woman, sick in bed with tularaemia (a word entirely new to her ears), "the name is beautiful." Having become a recognized disease of man the change of name from "plague-like disease of rodents" to "tularaemia" was welcomed, not only for scientific accuracy but also by the sick themselves, for what human being would not recover more quickly from the euphonious "tularaemia" than from the depressing "plague-like disease of rodents."

GLANDULAR TYPE OF TICK FEVER

Dr. H. E. Lamb of Gooding, Idaho, in a paper read before the South Idaho District Medical Association in April, 1923, used the phrase "glandular type of tick fever" to describe cases which were encountered in practice by himself and Dr. J. H. Cromwell. At that time they considered these cases as a type of Rocky Mountain spotted fever, and added that about 10 per cent of their cases of "tick fever" (fever following a tick bite) had been of the glandular type without eruptions; that the glands in some cases suppurated, while in others they did not, and that these patients were very sick and had fever for several weeks. The interpretation is justified that these cases of the "glandular type of tick fever" were tularaemia, since the serum of one of Drs. Lamb and Cromwell's early cases (J. N. B.) gave positive agglutination of *Bacterium tularense* (1:40), partial (1:80) at the Hygienic Laboratory on April 26, 1924; the onset of illness of this patient was in the spring of 1914, following a tick-bite on the left leg; swelling of the left inguinal glands and fever confined the patient to bed for two weeks.

TICK INFECTION AND TICK TRANSMISSION

Parker and Spencer (19) of the United States Public Health Service, in the course of their studies of Rocky Mountain spotted fever at Hamilton, Montana, recognized the agency of the common wood tick of Montana, *Dermacentor andersoni*, as a host and transmitter of tularaemia. Working in a fruitful field of tularaemia in Montana they have contributed abundantly to our knowledge of the subject. Their observations and demonstrations may be summarized as follows: (1) They suspected tularaemia in ticks in numerous instances, in 1922, on account of the gross lesions at death in guinea pigs, into which ticks has been injected as a routine test for the presence, in ticks, of the virus of Rocky Mountain spotted fever. (2) They isolated *Bacterium tularense* in May, 1923, from guinea pigs into which had been inoculated adult ticks collected in nature from vegetation in the Bitter Root Valley, Montana; similarly they found the infection in ticks collected from the horse, mountain goat, woodchuck, mountain rat and Columbian ground squirrel. Widespread natural infection

of the wood ticks of Montana, especially of the eastern portion, was soon shown. (3) They transmitted the infection among rodents by the wood tick, *Dermacentor andersoni*, and by the rabbit tick *Haemaphysalis leporis-palustris*. (4) They (20) demonstrated hereditary transmission of the infection by female ticks of the species *Dermacentor andersoni* through their eggs to the next generation. (5) They found the infection in nature in the snowshoe rabbit and the jack rabbit of Montana. (6) They (21) showed the susceptibility of seven other species of Montana rodents and of the coyote (22). (7) They (23) demonstrated *anti-tularense* agglutinins in their own blood and in the blood of four others of their laboratory personnel, all of whom contracted tularaemia in their laboratory, and in three of whom the direct cause was infected ticks.

During 1925 and 1926, 55 human cases (21) of tularaemia (47 confirmed by agglutination tests) were reported by physicians of Montana—the most which any state has reported. Of this number 13 were definitely due to tick bites, and in 10 others tick bite or contamination by tick tissues or excreta was the probable source. Dr. M. C. Pfunder (24), of Miles City, Montana, reported the first of these cases. Of the total cases, 18 were reported by Dr. B. C. Farrand of Jordan, Montana, and 14 by the Miles City Clinic (Drs. Garberson, Pfunder and Winter).

RABBIT FEVER

Dr. J. Lawn Thompson (25) of Washington, D. C., was the first to recognize a case of tularaemia in the eastern United States. His patient, E. N., was a market man who was engaged in skinning and dressing wild rabbits in the Washington market in November and December, 1921, at which time he suffered an attack of fever and prostration, accompanied by a painful enlargement of the axillary glands of one arm which lasted one month. Strangely, the patient diagnosed his own case, telling his physician that it was "rabbit fever" and added that "rabbit fever" was well known among market men. In June, 1922, his blood serum agglutinated *Bacterium tularense* at the Hygienic Laboratory in a dilution of 1:320.

Francis (26) isolated virulent *Bacterium tularense* from 7 of 914 rabbit livers examined in the Washington, D. C., market in January,

1923; that organism was also isolated from livers examined in December, 1924, and December, 1925. There have been 22 human cases of tularaemia traced to rabbits sold in that market. There have now been reported in the United States 243 cases due to skinning, dissecting or dressing wild rabbits.

OHARA'S DISEASE

Four articles, in Japanese text, deal with a disease of man occurring in Japan which was proven by Francis and Moore (31) to be tularaemia, although none of the four articles contains specific mention of tularaemia or of the published work of the American investigators of the latter disease. Two of these articles are by Ohara (27, 28), one is by Aoki, Kondo and Tazawa (29), and one is by Iwamoto, Muto and Aomura (30). Their dates of publication are between March 12, 1925, and July 10, 1925.

In the titles of their articles and in their statements of the source of the infection, the authors couple a disease of wild rabbits with a disease of man in the relation of cause and effect. Their clinical descriptions of 12 human cases agree even in minor details with the picture of tularaemia. Their descriptions of the microscopic changes of the lesions in human lymph glands are those of tularaemia. Their description of the macroscopic lesions in guinea pigs and mice is that of tularaemia. Their bacteriological and cultural studies show a failure to find the etiological element of the disease. Much mention is made by Aoki, Kondo and Tazawa of a spirochete-like organism.

The prompt occurrence of illness in Kondo and Tazawa, while engaged in performing necropsies of infected laboratory animals, is mentioned; this is in accord with the certainty of infection with tularaemia which has befallen eighteen workers in five laboratories in the United States and in one laboratory in England.

Proof of the identity of the American and Japanese diseases was furnished by Francis and Moore (31, 32) who, on seeing Ohara's first descriptions requested serums from recovered human cases for agglutination tests and fresh human lymph glands for isolation of a culture. These materials were promptly furnished by Ohara and they yielded complete serological and bacteriological proof of the identity of the

disease occurring in Japan and tularaemia occurring in the United States.

"Ohara's disease" was the convenient designation given by Francis and Moore to the Japanese disease as a mark of distinction to Ohara, not only for his keen clinical and epidemiological observations, but also for the priority which his description holds over all other Japanese publications on this subject. The name also serves as an added mark of distinction for Mme. Ohara, who courageously volunteered as an experimental subject to help prove the scientific conviction of her husband.

LABORATORY INFECTIONS OF MAN

The certainty of laboratory infection of man with tularaemia is one of the many unique features of the disease. No other disease has claimed among its victims so high a percentage of laboratory personnel (33). Only those have become infected who either have performed, or assisted at necropsies of infected guinea pigs, rabbits or white mice, or have held infected living rabbits or guinea pigs, or have handled infected living ticks; of such cases there have been 20.

The time which elapsed between the first exposure to infected animal or ticks and the onset of illness in 17 cases of laboratory infection was as follows:

Days—7, 9, 10, 14, 14, 14, 17, 43, 80, 94 and 98
Months—3 to 5, 3 to 5, 4, 9, 12 and 15

In one instance the sole time of contact with an infected guinea pig was one occasion of ten minutes, and in this case the first symptoms were noticed nine days after exposure.

Fifteen of these cases occurred in the laboratories of the United States Public Health Service as follows: Two (3) in the plague laboratory in San Francisco in 1911; two (34) in a field laboratory at Delta, Utah, one in 1919 and one in 1920; four (34) in the Hygienic Laboratory in Washington, D. C., one in 1920 and three in 1921; six (23) in the Rocky Mountain spotted fever laboratory at Hamilton, Montana, three in 1924 and three in 1925; and one (35) in the plague laboratory at Los Angeles, California in 1926.

Three cases (36, 37) occurred in the Lister Institute of Preventive

Medicine, London, England, in 1922, the source of infection of which was a culture of *Bacterium tularense*, isolated in Utah from a human case, M. S., and sent from the Hygienic Laboratory, Washington, D. C., March 25, 1922, at the request of the Institute for inclusion in their National Collection of Type Cultures. The Assistant Curator, the Curator and a member of the bacteriological staff of the Institute fell victims to tularaemia on July 12, September 15 and September 18, 1922, respectively. The procedure of carrying the infection on by animal passages habitually proved so dangerous that "by a brave discretion" it was given up by the Institute (38). "It was deemed inadvisable to continue the propagation of this dangerous organism in the National Collection" (39).

INDEPENDENT OBSERVATIONS

When reading the collected contributions which each has made to our knowledge of tularaemia, one is likely to credit the investigator with knowledge, at the time, of the printed work of his predecessors. As a matter of fact, many of the findings in tularaemia were made independently without such knowledge.

McCoy published his rodent disease in April, 1911, and Pearse published his human disease in March, 1911, and yet neither knew of the other's work until 1920.

Wherry and Lamb in 1913 carried the infection from Vail's eye case through twenty-four guinea pigs before they became acquainted with the work of McCoy and Chapin published in 1911 and 1912.

Francis in 1919 and 1920 isolated the infection from man and wild rabbits in Utah without knowledge that Wherry and Lamb had done the same thing six years before in Cincinnati; he was also without knowledge of Pearse's observations of 1911.

Martin's significant letter of 1907 emerged from a forgotten file only in 1925.

Ohara in Japan published his clinical and experimental observations in 1925 without knowledge of the American literature on the subject.

LOOKING BACKWARD

Physicians, on reading the recent articles on tularaemia have now looked backward and have plainly recognized the clinical picture of

the disease in cases of illness for which at the time no description could be found to fit. Fortunately, those observations of years before are capable of present-day verification, because of the persistence of *anti-tularense* agglutinins in the blood-serum of long-recovered cases of tularaemia. Physicians have recently sent to Francis at the Hygienic Laboratory for agglutination test, serums from cases which constituted diagnostic puzzles to them at the time of illness in years gone by; all of these serums reacted positively as follows:

18 years. G. W. W., patient of Dr. Ancil Martin, Phoenix, Arizona; onset in July, 1907. Positive (1:20) July 10, 1925.

17 years, 4 months. W. L. B., patient of Dr. W. L. Brosius, Sr. of Missouri; onset in October, 1909. Positive (1:160) February 19, 1927.

12 years. I. D. L., patient of Dr. Tom Kirkwood, Lawrenceville, Illinois; onset November 1, 1914. Positive (1:20) December 29, 1926.

11 years. H. H., a patient of Dr. V. M. Brian, St. Francisville, Illinois; onset in November, 1915. Positive (1:80) December 30, 1926.

11 years. J. I. B., patient of Dr. C. E. Harris, Basin, Wyoming; onset in 1915. Positive (1:160) August 13, 1926.

10 years. L. C. W., a patient of Dr. C. E. Harris, Basin, Wyoming; onset in August, 1916. Positive (1:40) September 15, 1926.

10 years. Mrs. H., a patient of Dr. C. E. Harris, Basin, Wyoming; onset July 26, 1916. Positive (1:40) July 23, 1926.

10 years. R. C. E., a patient of Dr. C. D. Carter, Thermopolis, Wyoming; onset in July, 1916. Positive (1:80) August 16, 1926.

10 years. J. N. B., a patient of Drs. Lamb and Cromwell, Gooding, Idaho; onset in spring of 1914. Positive (1:40), partial (1:80) April 26, 1924.

7 years. Mrs. E. H., a patient of Dr. Tom Kirkwood, Lawrenceville, Illinois; onset November 24, 1919. Positive (1:80) November 24, 1926.

6 years, 8 months. B. B. M., patient of Dr. J. E. Womack, Staunton, Virginia; onset, November 9, 1920. Positive (1:80) July 18, 1927.

6 years, 4 months. J. M. D. and Mrs. J. M. D., patients of Dr. C.

H. Davidson, Lexington, Virginia; onsets November 11 and 12, 1920 respectively. Both positive (1:40) March 25, 1927.

3 years, 6 months. E. T., patient of Dr. W. S. Kerlin, Shreveport, Louisiana; onset July 22, 1923. Positive (1:80) January 31, 1927.

CHRONOLOGY

The recognition of human cases of tularaemia is dependent on serological, cultural and clinical findings. Looking backward and utilizing these means of diagnosis the chronology of the first cases in man and of the first recognition of rodent infections has been arranged by states for 37 states of the United States, the District of Columbia and Japan as follows:

1907. Arizona: Martin (14, 15); Martin's letter September 19, 1907.
1908. Utah: Pearse (7); Francis (16); Francis (17) infection in Jack rabbits and ground squirrels.
1909. Missouri: Brosius (see above, page 106).
1910. California: McCoy (2) infection in ground squirrels. McCoy and Chapin (3) laboratory infections of man. Dieter and Rhodes (54) infection in wild rats.
1913. Ohio: Vail (8); Wherry and Lamb (11).
1914. Indiana: Sattler (9); Wherry and Lamb (12, 13) infection in Wild cotton tail rabbits.
Illinois: Kirkwood (1927) (see above, page 106).
Idaho: Lamb and Cromwell (see above, page 106).
1915. Wyoming: Harris (see above, page 106).
1920. Virginia: Davidson (see above, page 107).
1921. Washington, D. C.: Thompson, in Francis (25, 26).
North Carolina: Gage, in Francis (25).
1922. Tennessee: Francis (26) infection in cotton tail rabbits. Strain (1926).
1923. Montana: Parker, Spencer and Francis (19) infection in wood ticks and snowshoe rabbits; Pfunder (24).
Montana: Parker and Spencer (23) laboratory infections of man.
Louisiana: Kerlin (see above, page 107).
Japan: Ohara (27, 28).
1924. Mississippi: Martin (1924).
New Mexico: Anderson in Francis (25).
West Virginia: Hodges (1925).

1925. Texas: Adams and Carter (1925).
Oregon: Dietsche (see above, page 98).
Kansas: Lavan (1926).
Iowa: Whiteis and Anthony (1926).
Kentucky: Kavanaugh.
Pennsylvania: Maclachlan, Fetter and Cratty (1926).
Georgia: Dorsey and Waits.
Arkansas: Strain (1926).
Maryland: Flick (1926).
South Carolina: Wallace (1926).
1926. Nevada: Albert (1926).
Colorado: Covey, in Barry (1927).
Minnesota: Rutledge (1927).
Florida: Burns. Harper (1927).
Alabama: Mason and Mason (1927).
Nebraska: Barry (1927).
Michigan: Compere and McMillan (1927).
1927. North Dakota: Cornelius.
South Dakota: Cornelius.
Oklahoma: Nash.

ANTIQUITY

Tularaemia has existed in the United States, almost certainly in wild rabbits and man since 1907 in Arizona, and since 1909 in Missouri; and certainly in the California ground squirrel since 1910.

Ohara, on making inquiry of the villagers of the Abukuma Mountains in Japan, concluded that a disease simulating tularaemia existed among them for twenty years previous to 1925.

Ohara (27) refers briefly to a recently-found historical account of a disease which he thinks was tularaemia, described in 1837 by a Japanese physician, K. K. Homma (40), in his book of diseases. Ohara states that Homma, under the head of intoxication by rabbit meat, described in detail the incubation period and symptoms of a disease which, according to Homma, had not theretofore been described. Although Homma's original work has not yet become accessible to us, that imperfect account is nevertheless remarkable when one considers the diagnostic darkness that prevailed in Japan one hundred years ago.

If one is inclined to conjecture he might ask the meaning of Leviticus XI, 4–8, and especially why only two of the herbivorous rodents (hare and coney) should be thus singled out for inclusion in a class which was unclean, and whose carcasses should not even be *touched*. Some very good physical reason doubtless existed for the biblical prohibition, against even touching a dead rabbit. Let us hope that the reason will yet be found hewn on some stone or scrawled on some papyrus.

SUMMARY OF RECENT KNOWLEDGE

During 1924, 1925, 1926 and 1927 the number of states of the United States in which human cases of tularaemia were recognized increased from 6 to 37, and the number of case reports increased from 15 to 407; in addition, the dentity of Ohara's disease, occurring in Japan, and tularaemia occurring in the United States, was demonstrated. This indicates that physicians have learned to recognize a disease which has doubtless passed unrecognized for years.

The great reservoir of infection is wild rabbits. The infection has not been found in nature in domestic rabbits raised in rabbitries (41).

The principal modes of transmission to man are: (1) By the bite of the horse fly, *Chrysops discalis*. (2) By the bite of the wood tick, *Dermacentor andersoni* Stiles. (3) By contamination or self-inoculation of ones' hands or conjunctival sac with portions of the internal organs or body fluids of infected rabbits flies or ticks. (4) By the bites of the coyote, ground squirrel and hog—one case by each; presumably the mouth parts of these animals were contaminated by infected rabbits which they had eaten. (5) By the bite of a tick in southern United States (species undetermined).

In studying 407 case reports four clinical types are noted:

(1) *Ulcero-glandular*, the primary lesions beng a papule, later an ulcer of the skin and accompanied by enlargement of the regional lymph nodes—272 cases.

(2) *Oculo-glandular*, the primary lesion being a conjunctivitis and accompanied by enlargement of the regional lymph nodes—25 cases.

(3) *Glandular*, without a primary lesion, but with enlargement of the regional lymph nodes—16 cases.

(4) *Typhoidal*, without primary lesions and without glandular enlargements—24 cases.

Unique features. The following outstanding features of tularaemia deserve special mention: (1) The certainty of infection of laboratory workers. (2) The persistence of agglutinins in the bood of long-recovered cases. (3) The cross-agglutination (42) of *abortus* and *melitensis*. (4) The granulomatous (9, 43, 44, 57) character of the lesions in man as contrasted with the lesions (37, 48, 49, 55, 56) in animals. (5) The cystine (45, 46, 47) requirement of the organism in culture medium. (6) Its pleomorphism. (7) Its penetration of the unbroken skin. (8) Its invasion of fixed tissue cells—the hepatic cells of a mouse (36, 37, 48), and the intestinal epithelium of the tick (49) and bed bug. (9) Its hereditary (20) transmission through the egg of the tick to the next generation of ticks. (10) The great variety (2, 4, 18, 19, 50, 51, 52, 53) of insect hosts. (11) The great variety (2, 3, 4, 21, 22, 54, 56) of animal hosts.

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THE ETIOLOGY AND PREVENTION OF MEASLES[1]

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As measles is the most prevalent of the diseases of infancy and early childhood, and also predisposes to a complicating bronchial pneumonia, it is one of the two most fatal of the communicable diseases of early childhood, and its prevention has been eagerly sought by clinical and laboratory investigators. The ideal in their mind is to discover the germ and prepare a vaccine and an anti-serum.

The earliest work was on the location of the virus and the possibility of getting a vaccine from the skin, the mucous membranes or the blood.

Hektoen (1) in a review of this subject in 1905 sifts the evidence given of the success of a number of investigators of transmitting the disease to human beings by inoculation, and concludes that with few exceptions the positive results are without real significance. In many cases exposure to measles was not excluded, in others the disease appeared too early. One of the most careful attempts was made by Mayr. If we accept his results it may be concluded that in measles nasal mucus and cutaneous scrapings, mixed with blood, from cases in the early development of the rash contain the virus of the disease. In three cases he used fresh nasal mucus and applied it to the membrane of the nose of susceptible children. In two of these the eruption came out on the fourteenth day. In the other no infection developed. The disease in both was mild. In others he applied to scratches in the skin the blood, mixed with skin particles scratched from the center of a rubeolous spot. In six of these children he was successful. In none of these cases was there any change at the site of the inoculation and he concludes that as it is impossible to localize the process as in vaccination against smallpox, there is no practical importance in trying to inoculate against measles.

[1] January 24, 1927.

Starting with a knowledge of this work, Hektoen proceeded to make a more definite test as to the presence of the virus in the blood of measles cases. He took great care to avoid any possibility of natural infection in those upon whom he made the test. The first volunteer was injected with the diluted blood taken from a nine year old boy whose rash had first appeared forty-eight hours before and was then at its height. In one flask containing 50 cc. of ascitic broth (ascitic fluid one third) 1 cc. of blood was added and in another 3 cc. were added. The two flasks were placed in the incubator at 37°C. for twenty-four hours. At the end of this time the contents of both flasks appeared sterile, the corpuscles having settled and the supernatant fluid being clear. Subcultures made from the flasks on ascitic agar and blood serum under both aerobic and anaerobic conditions remained sterile. Four cubic centimeters of the flask in which 3 cc. of blood had been added were injected under the skin of the chest of a healthy medical student who had volunteered for the experiment. On the thirteenth day after the injection his temperature rose to 101°, and on the next day to 103°, when a red, papular, blotchy eruption broke out which was considered a typical measles rash. The second test was made with blood withdrawn from a young woman suffering from an uncomplicated attack of measles. It was added to ascitic broth and treated in the same way. No visible growth appeared in the flask. After twenty-four hours in the incubator, 5 cc. were removed and injected into a volunteer. On the eleventh day the temperature rose to 99.8° and a mild conjunctivitis appeared. On the thirteenth day there was a slight cough, the temperature rose to 103° and on the fourteenth day a typical rubeolous eruption appeared. The rash consisted of pink macules and papules, and was characteristic in every way. Cultures from the flask of ascitic fluid blood made on the thirteenth day remained sterile.

His conclusion is that the virus of measles is present in the blood of patients during at least the first thirty hours of the eruption; furthermore that the virus retained its virulence for at least twenty-four hours when such blood is inoculated into ascitic broth and kept in the incubator at 37°C. He adds: "This demonstration shows that it is not difficult to obtain the virus of measles without other microbes and in such form that it may be studied by various methods." The

fact that not only the blood showed no visible bacteria, but also cultures made from this infectious material is of importance.

Following Hektoen's experiments on man a number of experiments were made upon monkeys. In 1911 Anderson and Goldberger (2) showed that the blood of persons sick with measles was infectious from at least shortly before the eruption appeared until at least twenty-four hours after its appearance, but that at that time the blood was already becoming less infectious. Later experiments by Anderson confirmed some earlier work and that at least in monkeys the desquamated skin was not infectious. They found that the virus of measles passed through a Berkefeld filter, that it resisted desiccation for twenty-four hours, that it was destroyed by heating to 55°C. for fifteen minutes.

Herrmann of New York City has proposed a very interesting method of inoculating infants intranasally with the secretion obtained from the nose of an infant during the early stage of the disease. He proposes to do this inoculation during the sixth or seventh months of life before the infants have entirely lost their inherited immunity. This method, in our opinion, is not practicable for general use.

The experimental studies up to the work of Tunnicliff indicated that the virus was not visible by ordinary methods, that it could pass readily a Berkefeld filter and that it produced in monkeys an infection resembling atypical cases of measles.

In 1917 (3) Tunnicliff described a micrococcus which she obtained almost regularly from the blood and secretions of measles patients, both during the development of the rash and in the late pre-eruptive stages.

She had considerable difficulty in getting the microörganisms to grow on ascitic fluid bouillon or on blood serum, and so accounted for Hektoen's failure to get cultures of her streptococcus from the blood, which produced measles. She obtained the best results in semi-coagulated horse serum and whole blood-ascitic-dextrose agar shake cultures. Anaerobic plates and hemolyzed blood-ascitic fluid-dextrose shake cultures were fairly satisfactory.

Blood cultures were made from fifty cases of true measles in the pre-eruptive stages. In 42 of the 50, the small micrococcus was obtained. The cocci were found, however, in all of the last 15 cases.

This suggested that the occasional early failures were due to less suitable technique. Sometimes in the shake plates, made from the cases, "innumerable" colonies appeared. The evidence of visible growth appeared in the tubes in from one to twenty-one days, generally in from five to fifteen days. Many of the cultures failed to grow on subculture. One strain remained anaerobic, the others became aerobic. Successful subcultures on blood agar plates showed small greenish colonies giving a decidedly green color to the medium. Four of the strains on dextrose blood agar gave larger moister colonies than the others. These four did not decolorize milk; the others produced acidity and some coagulation. In subcultures the organisms were frequently in short chains. Cultures of the diplococcus passed the Berkfeld filter "N." They resisted drying for twenty-four hours. Before the eruption appears these cocci are the only ones found in the blood; later in the disease other bacteria are present.

In 1921 it was found by Nevin, Grund and Bittman in my laboratory that not only monkeys, but rabbits could be infected with the nasal discharges from measles patients and with their blood if the material was taken early in the disease. The disease was peculiar in that Koplik spots and rash developed as early as the third day. The rash was followed by desquamation. The fifth culture transfer from filtered nasal washings was infectious, which indicated that the virus developed in the culture fluid for five successive cultures. The infecting dose contained only 0.0001 cc. of the original mucus. One-half cubic centimeter from the 10 cc. contained in the tube was transferred in each transplantation.

Tunnicliff reported in 1925 that the same symptoms and lesions as are produced by the inoculation of washings of the nose and throat of patients with measles have been observed to follow the inoculation of the measles diplococcus in monkeys, guinea pigs and rabbits. Rabbits successfully inoculated with the diplococcus have shown no symptoms when reinoculated with fresh measles material. Green-producing diplococci isolated from the blood and lungs of rabbits successfully inoculated with the measles diplococcus also gave rise to Koplik spots and exanthem when injected into other rabbits. She states that the chance of the selective transfer of an unknown virus by the green-producing diplococcus appears small, because diplo-

coccus cultures, originally isolated from single colonies, have produced a reaction in rabbits in the seventh generation, while rabbits similarly inoculated with the second generation of cultures of staphylococci, other green and hemolyzing streptococci from the same plates developed no symptoms of measles. She then turned to discover what proof could be obtained from skin reactions in man following intracutaneous injections of mixed toxin and dead culture, or, as she modestly put it, "the skin reaction to the diplococcus found by me in measles has been studied with a view to obtaining light on its relation to measles." She found that Berkefeld W filtrates of aerobic and anaerobic cultures, grown from twenty-four hours to six days in broth with and without ascitic fluid, failed to produce any reaction. Killed organisms suspended in salt solution also failed to give convincing reactions. She then tried a method similar to that used by Gabritschewsky in his streptococcus immunization against scarlet fever, which produced skin reactions in persons who had not had scarlet fever. A few drops of ascitic fluid were added to each 5 cc. of 1 per cent dextrose broth and cultures grown anaerobically under oil; the cocci in the broth were then killed by the addition of 0.5 per cent phenol (carbolic acid) at room temperature. Usually the cocci were killed in twenty-four hours. Anaerobic cultures produced better results than aerobic, and twenty-four-hour cultures gave better antigens than five or six-day growths.

Twenty-one strains of bile insoluble green-producing diplococci have been tested on rabbits. Five strains were isolated at the onset of measles, one from the blood, and four from the respiratory tract; one strain was isolated from the blood of a goat inoculated intravenously with measles diplococci; fifteen strains were isolated from late cases of measles, from scarlet fever, German measles, acute tonsilitis, the mouth of a normal goat and the normal human throat. The six measles antigens gave marked reactions in normal rabbits, but no reactions in rabbits immune to measles.

Neutralization experiments. Neutralization experiments have been made with the strains that gave positive tests. The measles antigens were mixed with equal parts of salt solution, of normal goat serum, of antidiplococcus goat serum and of convalescent human measles serum. The serum of two normal rabbits and of one rabbit im-

munized with the measles coccus was tested with one measles antigen, prepared from the same organisms used in immunization. The culture medium was also used as a control. Antigens from other sources were mixed with salt solution and convalescent human measles serum. After incubation for three hours, 0.2 cc. of the mixture was injected intracutaneously in normal rabbits. Normal goat serum did not neutralize the measle antigens. Both convalescent human measles serum and anti-diplococcus goat serum neutralized the measles antigens. The two strains isolated late in measles, the strain from the normal throat and the one from tonsilitis were not neutralized by convalescent human measles serum. The serum of the two normal rabbits tested neutralized the measle antigen partly, while the immune rabbit serum completely neutralized it.

Since the measles diplococcus antigen gave definite cutaneous reactions in normal rabbits, similar tests were made in human beings. Two different measles strains were used, but most of the experiments were made with a culture isolated two years previously with which Koplik spots, eruptions and fever had been produced in rabbits. The antigen was diluted with salt solution to a point that gave no reaction in persons who had previously had measles, and generally a dilution of 1:40 was suitable. No reaction occurred with the control anaerobic ascites broth culture mediums, to which phenol (carbolic acid) and salt solution were added as in the antigens, except sometimes a redness 0.3 cm. in diameter at the site of the needle prick. Twenty-eight persons who gave a history of measles or were convalescing from measles showed no reaction to the measles antigen except occasionally the same redness as caused by the control injection of culture mediums. One person with a history of measles reacted positively. A patient with the measles eruption just out on the face gave no reaction. Twenty-six persons, who had not had measles, gave a definite reaction in from four to forty-eight hours, generally in twenty-four hours, in the form of a circumscribed area of erythema of varying intensity, from 1 to 2 cm. in diameter, as a rule with slight infiltration. The reaction in some instances has been followed by pigmentation and desquamation; generally it disappeared in from twenty-four to forty-eight hours, but occasionally it persisted for four or five days.

The ages of the persons tested who gave a history of having had measles varied from fifteen months to fifty years, of those not having measles from six months to ten years. The sexes were practically the same in both groups.

A few neutralization experiments were tried on persons who had not had measles. She found that to get complete neutralization with convalescent human measles serum in human beings, great great care must be taken to get the correct dilution of the antigen and to inject exactly the same amounts of each mixture. Serum from a person with a negative history of measles who showed a positive skin reaction was used as the control serum. The measles. antigen was mixed with equal parts of salt solution, control serum and convalescent human measles serum. The mixtures were incubated and injected as previously described. In twenty hours the mixtures with salt solution and control serum produced a circumscribed area of erythema 1.5 cm. in diameter; the mixture with convalescent serum produced no reaction.

Conclusions by Dr. Tannicliff. Anaerobic dextrose broth cultures of the green-producing diplococcus found in measles, killed by 0.5 per cent carbolic acid, appear to produce a skin reaction in persons who have not had measles, but not in measles patients after the appearance of the eruption, or in 96 per cent of persons who gave a history of measles. The measles antigen is neutralized in persons who have not had measles, by convalescent human measles serum, but not by the serum of a person with a negative history of measles. Reaction occurs also in normal rabbits, while rabbits immunized against measles fail to react. The measles antigens are neutralized in rabbits by convalescent human measles serum and by the serum of goats recovering from the reaction produced by measles diplococci, but not by normal goat serum. Green-producing cocci from other sources generally give no reactions in rabbits, but the strains that do, produce similar reactions in both immune and in non-immune rabbits and are not neutralized by convalescent human measles serum. Normal rabbit serum neutralizes measles antigen partly, immune rabbit serum completely neutralizes it.

These results indicate that the Gram-positive, green-producing diplococcus found in measles is of etiologic significance.

In the January number of the *Journal of Infectious Diseases* she reports that the serum of a goat convalescing from the reaction produced by an inoculation of the green-producing streptococci protected rabbits against a subsequent injection of infective material from measles. The rabbits injected with normal goat serum and untreated rabbits showed some or all of the symptoms of measles after the injection of the measles infective material.

Used in children the serum only protected when given during the first two days after exposure.

Development of antibodies in goats for preventive use. The organisms were grown in 1 per cent dextrose broth twenty-four hours; the cultures were centrifugalized and the cocci suspended in salt solution. Later, broth cultures of the cocci and also filtrates of six-day cultures, in 1 per cent sheep blood dextrose broth, were injected. Small doses were given at first, but by the end of three months the growth from 200 cc. of broth was injected into each goat. All injections were made intravenously.

At the end of three months, they found the serum of the two goats contained about the same amount of antibodies. The serum agglutinated the three immunizing strains at from 1:2500 to 1:5000, and contained from fourteen to twenty-four times more opsonins than normal goat serum. After the first three months of immunization, the antibody content of the serum reached its height and then fell slightly and remained about stationary.

By intracutaneous tests in normal rabbits, the serum was found to neutralize the action of both killed measles diplococci (intracellular toxin) and filtrates from measles diplococcus cultures (extracellular toxin), while normal goat serum had no such effect.

They then tried rash extinction tests. The intracutaneous injection of 1 cc. of immune goat serum into two persons with Koplik spots, but before the appearance of any rash, almost completely prevented the development of the measles rash over an area of about 2 cm. around the site of injection. As is well known Debré, Bonnet and Broca injected subcutaneously from 1 to 5 cc. of convalescent human measles serum at the beginning of the period of invasion, just as the catarrhal symptoms and Koplik spots appeared, but before the beginning of any eruption and found that when the rash appeared

there was inhibition about the point of injection varying in size with the amount of serum injected. Normal goat and human serums failed to produce any inhibition.

Hoyne and Gasul used this immune goat serum in thirty-nine children over six months of age, and concluded that if the serum was administered not later than the fifth day of exposure (counting the date of onset as the first day of the disease) protection seemed assured in about 90 per cent. Those, who received serum early, but were not wholly protected, developed an attenuated form of the disease.

A recent report (4) gives the results of using immune goat serum in 105 additional persons, with a negative history of measles, but subjected to a definite exposure to the disease.

The following is a summary of their findings: 1. Goats have been immunized with green-producing measles diplococci and their filtrates, and an antibacterial and antitoxic serum was produced.

2. From 4 to 6 cc. of immune goat serum was given to children one year old or older and to a few nurses, with a negative history of measles, after a definite exposure to measles. All persons who did not receive serum, and all who received serum five days or more after exposure, developed measles. Goat serum prevented measles in 45 per cent of persons who received serum on the fourth day after contact with measles patients, and in 97 per cent of those who received it within the first three days after exposure.

3. All infants under one year of age who received serum after the fourth day after exposure developed measles. Ninety-eight per cent of infants given serum within the first four days after exposure failed to show any signs of the disease.

4. Reactions to the goat serum were observed in 12 per cent of those injected.

5. Although the duration of passive immunity with immune goat serum as with human convalescent measles serum is only a few weeks, the serum appears to be useful in preventing measles in very young and sick children, and in stopping epidemics in institutions where the inconvenience of an epidemic is great and the mortality may be high.

I have had only a slight opportunity to test the effect of preventive inoculations. The first group of cases was interesting in that neither

the children injected with the immune goat serum nor those left as controls developed the disease. My second opportunity was not a satisfactory one since the children had been exposed for at least five days. The injection of the children did not prevent the development of measles or apparently modify the attack. This was a goat antitoxin developed from the Ferry strain and sent to me by Dr. Ferry.

The published reports of Tunnicliff and Ferry certainly present very impressive evidence of the etiological significance of her diplococcus. There were, however, several difficulties which prevented me from being completely convinced. It seemed difficult to understand how a diplococcus which appeared in enormous numbers in the discharges from the eyes, nose and throat during the catarrhal stage of measles should be absent in cases, as shown by its lack of contagiousness, from the upper respiratory tract during the period of incubation. If measles were due to this diplococcus it would seem probable that like diphtheria and scarlet fever soon after the transfer of the infecting microbe, it would begin to develop and produce symptoms and spread infection.

Again in almost all diseases due to bacterial infection there are a greater or less number of cases in which the infecting microbes persist. Cultures, as well as transmitted infection to others, reveal this. Measles like small-pox, mumps, rabies, yellow fever and most other diseases supposed to be due to filterable viruses has a long period of incubation when it is not communicable and then when convalescence is established it suddenly ceases to spread contagion.

While impressed by the evidence submitted by Tunnicliff and Ferry I was still doubtful and I felt it wise to undertake seriously an attempt to corroborate her findings. In order to make these studies possible I applied for and obtained a grant of money from the Milbank Memorial Fund. Dr. Anna Williams, Miss Wilson and Miss Gurley and a number of technical assistants have worked together with me on this problem.

Our first endeavor was to discover through cultures whether the diplococci were regularly present in the pre-eruptive and eruptive stages and whether the strains were the sane in the different cases.

Table 1 gives the results, so far as the appearance of colonies on blood and ascitic agar indicate identity.

The results from the etiological standpoint are perplexing. Eighty-four per cent of the measles cases gave characteristic colonies on both blood and ascitic agar, while in nine control cases characteristic colonies were not found. They were absent, however, in 16 per cent, and their persistence during the period of the fading rash was somewhat disquieting, since the cases had reached a stage when they were supposed to be but slightly or not at all communicable.

TABLE 1

Showing percentage of cases from which green streptococci (non-hemolytic) were isolated at various stages of measles

STAGE OF DISEASE	NUMBER OF CASES	PERCENTAGE OF CASES FROM WHICH GREEN COLONIES WERE ISOLATED	GREEN STREPTOCOCCI		NEGATIVE
			Positive*	Doubtful	
			Green and ascitic colonies like Tunnicliff	Green colonies like Tunnicliff ascitic colonies not like Tunnicliff	Colonies not green. Morphology of colonies like Tunnicliff. Ascitic colonies not like Tunnicliff.
			Number of cases		
		per cent			
Pre-eruptive	20	70	13	2	5
First day rash	19	89	16	1	2
Second day rash	11	72	7	1	3
Old rash	7	71	5	0	2
Controls: So-called influenza	9			9	

* The cultures in our "positive" column correspond to the description given by Tunnicliff of the colonies isolated from rubeola. The following is her description: on blood agar the colonies are small punctate, green. On ascitic agar, the colonies are small, round, homogeneous, smooth-edged.

Twenty-two of these strains, together with the Tunnicliff and Ferry strains sent us by these investigators were studied as to their action on carbohydrates. Six different groups were found, only two of which contained many cultures, namely the Tunnicliff and our 67-T. It is striking that the Ferry and Tunnicliff strains are different as to their actions on salicin and insulin. These findings are somewhat disconcerting and rather suggested the possibility that their diplo-

cocci are complicating microörganisms. We then tested different strains for their reaction to the agglutinin developed by the Tunnicliff strain, the Ferry strain and our 67-T strain (see table 3).

The rabbit blood serum which had been removed from the rabbit treated by injections of the Tunnicliff strain agglutinated strongly only one of the strains other than the Tunnicliff and only one other in very low dilution. The serum from the Ferry rabbit serum

TABLE 2

Twenty-two strains typed by carbohydrates as compared with Tunnicliff's and Ferry's

TYPE	MALTOSE	SALICIN	INULIN	MANNITE	RAFFINOSE	NUMBER OF OUR STRAINS IN THIS TYPE	
						Number	Stage of disease
Tunnicliff	+	+	+	−	+	6	2 pre-eruptive 3 first day rash 1 eighth day convalescence
Our 2. E	+	−	+	−	−	2	1 pre-eruptive. This is tonsil of type culture case 1 third day of rash
5. T	+	−	+	−	+	2	Fourth day of convalescence
4. T	+	+	+	−	−	0	
67. T	+	+	−	−	+	7	1 pre-eruptive 1 first day of rash 5 second day of rash
Ferry	+	−	−	−	+	1	Eleventh day of convalescence

The strains show in this table are similar to Tunnicliff's on blood-agar, ascitic-agar and in bile test.

agglutinated 2 of the 12 strains, and the serum from our 67-T none of the seven strains tested. We then tested the strains by agglutinin absorption and found the same results as by direct agglutination (see table 4).

These results are not incompatible with the possibility that while these strains differ so markedly in their reaction to specific agglutinins that they may produce the same toxins. We know that there are many different agglutinative types of diphtheria bacilli, scarlet fever

streptococci and pneumococci, but the great diversity of these strains suggests that they, like the influenza bacilli which have the same great diversity, may be only complicating pathogenic bacteria.

When the work was begun we planned to make cultures from a few of the cases from time to time from the beginning of the disease

TABLE 3

Comparison by direct agglutination of our green streptococci with Tunnicliff's and Ferry's

The cultures in this table were isolated from various stages of measles

STAGE OF DISEASE	BACTERIAL SUSPENSIONS	AGGLUTINATING SERUMS						
		Tunnicliff			Ferry 01860		Our 67-T	
	Strain number*	Rabbit serum number	Titer with homologous antigen	Titer with other strains	Titer with homologous antigen	Titer with other strains	Titer with homologous antigen	Titer with other strains
	Tunnicliff	20	3,200		1,600	—	3,200	3,200
	Ferry 1		3,200	—	1,600		3,200	—
	Ferry 2		3,200	—	1,600	1,600	3,200	—
Pre-eruptive.....	67-T	31	3,200	3,200	1,600	—	3,200	
	2-E	20	3,200	—	1,600	—		
	T		3,200	—	1,600	—		
	4-T	C	800	—	1,600	1,600		
	9-E		800	—	1,600	—		
	27-E	20	3,200	100	1,600	—	3,200	—
	33-T		3,200	—	1,600	—	3,200	—
	91-E	20	3,200	—	1,600	—	3,200	—
First day rash.....	1-E	20	3,200	—	1,600	—	3,200	—
	N		3,200	—	1,600	—	3,200	—
	18-E	C	800	—	1,600	1,600		

* Explanation of strain number: The numeral refers to serial number of the case, the letter to source of the culture: E (eye), N (nose), T (tonsil).

— means no agglutination in 1:100 dilution.

until after convalescence but in the mass of work the making of the later cultures was forgotten until June when the cases suddenly fell off. We had intended to test the early and later cultures from the same case for their identity in relation to specific agglutinins. This work is now being undertaken, but it was impossible to complete any

of the cases in time to make a report to you at this time. We can state, however, that in three cases of measles the green diplococci persisted up to the tenth, twenty-first and twenty-third day after the appearance of the rash, and that, so far as cultural appearance could determine, the diplococci which appeared in the first cultures per-

TABLE 4

Our green streptococci from measles compared with Tunnicliff's and Ferry's by agglutinin Absorption

STAGE OF DISEASE	ABSORBING CELLS	AGGLUTINATING SERUMS				
		Tunnicliff			Ferry 01860	
	Strain number	Rabbit serum number	Titer with homologous antigen before absorption with cells listed under "strain number"	Titer with homologous antigen after absorption	Titer with homologous antigen before absorption	Titer with homologous antigen after absorption
	Tunnicliff	20	3,200	—	1,600	1,600
	Ferry 1		3,200	3,200	1,600	—
	Ferry 2		3,200	3,200	1,600	—
Pre-eruptive.....	67-T	20	3,200	—	1,600	800
	2-E		3,200	3,200	1,600	1,600
	T		3,200	3,200	1,600	400
	4-T	C	800	800	1,600	1,600
	9-E		800	800	1,600	800
	27-E	20	3,200	1,600	1,600	800
	33-T		3,200	3,200	1,600	400
	91-E		3,200	3,200	1,600	800
First day rash.....	1-E		3,200	3,200	1,600	1,600
	N		3,200	3,200	1,600	1,600
	18-E	C	800	800	1,600	200

sisted to the final cultures (table 5). If further investigation proves them to be identical, it would require conclusive proof to make us accept them as the cause of measles, for it is well established that cases of measles are not communicable at such a period after convalescence and we have no knowledge of such a rapid loss of virulence in convalescence.

Drs. Tunnicliff and Ferry both claim that when the toxin or toxin and dead organisms are used in proper dilution in intracutaneous tests that they are diagnostic between immunity and lack of immunity to measles.

I have observed the results of tests in hundreds of young children some of whom have had measles and some of whom have not, and I have been unable to obtain distinctive results. Drs. Schroder and Zingher have had very similar results.

TABLE 5

Showing percentage of green streptococci in cultures from convalescent measles

CASE NUMBER	DAYS CONVALESCENT	EYE		NOSE		TONSIL	
		Amount growth	Per cent green	Amount growth	Per cent green	Amount growth	Per cent green
98	6	+	100	+++	0.1	+	100
	8	+	100	+	100		
	21	+	90	+	75	+++	95
99	11	++	95	++	90	++	99
	16	No growth		±	95	±	99
	23	+	45	+	25	++	50
100	6					+	50
	14					++	50
101	3					±	100
	7					+	50
	10					±	100

± = scant growth; + = moderate growth; ++ = abundant; +++ = profuse.

Three years ago with Freeman and Valentine I tried to see if it were possible to get in some medium the development of some toxin in cultures from filtered nasal secretion of early cases of measles. In only one case did we get a toxin, and this curiously enough was in a culture in which a diplococcus like the Tunnicliff diplococcus had passed the filter. This gave us fairly distinctive differences between susceptible children and those who had recently recovered from measles. Those who had not had it recently reacted quite irregularly.

It seemed to me, therefore, that there might have been some reac-

tion to the toxin of the diplococci, but that this in no way proved that they were the original etiological factor. Table 6 gives a characteristic test. It is seen how irregular the reactions were. Certainly they would not suffice to test the immunity of the children.

Tunnicliff in her early publications distinctly stated that her diplococcus did not produce a toxin. Ferry obtained from the blood

TABLE 6

Tests made with Tunnicliff measles toxin, Willard Parker

CASE	AGE	TOXIN 1:20	DILUTIONS 1:40	TOXIN 1:10 āā CONVALESCENT SERUM 1:2	BROTH CONTROL 1:20
		3	3		
"Susceptibles," i.e., those who never had measles					
1	4 years	1.0 × 1.0 P	1.0 × 0.7 PP	0.8 × 0.8 P	
2	16 months	0.4 × 0.4 P	0.4 × 0.4 P	1.5 × 1.5 P	0.5 × 0.4 P
3	2 years	0.4 × 0.3 P	0.3 × 0.3 P	0.5 × 0.5 P	0.2 × 0.2 P
4	15 months	1.5 × 1.5 P	1.0 × 1.0 P	0.6 × 0.6 P	0.5 × 0.5 P
5	14 months	0.5 × 0.4 P	0.7 × 0.6 P	0.5 × 0.6 P	0.3 × 0.4 P
6	4 years	1.5 × 1.5 P	2.0 × 2.0 P	0.5 × 0.5 P	
7	6 years	0.5 × 0.6 PP	0.3 × 0.3 PP	0.9 × 0.9 P	
"Non-susceptibles," i.e., the following children give a definite measles history					
1	3 years	1.2 × 1.1 P	0.9 × 1.1 P	2.5 × 2.5 BP	
2	2½ years	0.7 × 0.8 P	0.5 × 0.6 P	0.6	
3	2½ years	1.2 × 1.3 P	0.7 × 0.8 VPP	1.5 × 1.7 PP	0.5 × 0.4 P
4	2 years	0.5 × 0.5 P	0.4 × 0.4 P		0.2 P
5	1 year	1.2 × 1.2 P	1.5 × 1.6 P	1.5 × 1.4 P	
6	3 years	0.2 × 0.2 PP	0.2 × 0.2 PP	0.6 × 0.7 P	
7	4 years	1.5 × 1.5 P	0.4 × 0.5 PP	1.0 × 1.2 BP	

The tests were read 18 hours. 1.0 × 1.0 = diameters in centimeters.
P = pink; BP = bright pink; PP = pale pink; VPP = very pale pink.

of cases of measles a Gram-positive, aerobic, green producing streptococcus which made a very definite extracellular toxin. One-tenth cubic centimeter of a 1:400 dilution introduced in the skin produced a reaction. He named it *Streptococcus morbilli*. He obtained similar results to those already noted by Tunnicliff, but in addition he obtained an antitoxin for the soluble toxin. When mixed with the toxin it neutralized it.

In our hands both the Tunnicliff culture, the Ferry culture and our cultures produce soluble toxins, and when injected into animals antitoxin is produced. They are in all probability strains of the same group of microörganisms.

Effect of intracutaneous injections of the serum of immunized goats. Tunnicliff describes the result of injecting her diluted immunized goat serum intracutaneously into children before the measles rash has developed, and notes that, just as has been shown to occur with convalescent measles serum, the injection of serum from goats which have received injections of her diplococcus antigen inhibits the development of the rash. Long before her paper appeared I had

TABLE 7

Measles extinction tests. Area blanched

NUMBER OF CASE	HUMAN MEASLES CONVALESCENT SERUM 1:10	GOAT SERUM, OUR STRAINS 1:10	GOAT SERUM, TUNNICLIFF STRAIN 1:10	GOAT SERUM, FERRY STRAINS 1:10	CONTROL ANIMAL SERUM 1:10	CONTROL ANIMAL SERUM 1:10
5	2.0 × 2.0 F	2.0 × 2.0 M			3.0 × 3.5	1.5 × 1.5 F
6	4.0 × 5.0	4.0 × 3.0			3.0 × 4.0	
9	4.0 × 5.0	3.0 × 3.0	2.0 × 3.0	4.0 × 3.0		
4	3.0 × 3.0 M	3.0 × 3.0 M	3.0 × 3.0			
9	4.0 × 5.0 M	3.0 × 3.0	2.0 × 3.0	4.0 × 3.0		
12	4.0 × 4.0	3.0 × 3.0		1.0 × 1.0		

F = faint; M = marked blanching.

tried her goat serum, the Ferry serum and serum from goats immunized with our strains intracutaneously in children. The results with all these serums were striking and for a time I felt that we had strong evidence as to the specificity of the diplococci. In scarlet fever in which intracutaneous injections of convalescent human serum of antitoxin developed in the horse blanches the developed rash, I think we are right in thinking it is due to a direct antitoxin action. In preventing the development of the measles rash I am less certain that this is a specific antitoxin reaction. Having obtained these striking results I tried the serum of a goat which had been immunized to scarlatinal streptococci and one which had received diphtheria bacilli and one which had received, so far as known, no injections. The

results were surprising. The serum from one of the control goats, when given intracutaneously, inhibited the rash almost as well as did the convalescent measles serum or the Tunnicliff serum, and two of the others had definite, but not so decided action. Some of these tests are shown in table 7.

In 1921 de Cristina announced that he had obtained from cases of scarlet fever and measles minute anaerobic diplococci which grew in a special manner in special culture media. Later Caronia joined in the investigations. The organisms were found in blood, bone narrow, spinal fluid, urine, throat, post scarlatinal abscesses and desquamated skin. They were obtained in pure culture directly from the first four materials and through filtrates from the last three. They grew more quickly and abundantly when obtained early in the disease and when grown in Tarozzi-Noguchi medium.

Several other media are recommended, but not as highly as the above.

The medium in each tube is covered with a thick layer of sterile vaseline. After inoculation, the first change in the medium may occur in twenty-four hours to nine days as a slight haze about the piece of tissue. This cloud gradually increases and a finely granular precipitate collects about the bottom and sides of the tube. The medium becomes entirely cloudy in about ten to fifteen days. Then the cloud settles, and at about the twentieth day a clear zone is distinct.

The organisms appear as rounded single and diplococcus forms, from very minute to quite large forms. The intense cloudiness and the filtrability are evidence of ultramicroscopic forms. Many controls were used, and no results were obtained except from scarlet fever and measles cases.

Prophylactic vaccine. Made from heavy growth, 0.5 per cent phenol added, and put in 2 cc. vials. Three intramuscular injections of 2 cc. each are given on alternate days. No special disturbance noted. Injections produce immunity even when given directly after exposure.

The work of de Cristina and Caronia has been observed by a number of bacteriologists and clinicians and they have been unable to detect any errors, on the other hand, no one outside of Italy has been able to repeat their findings. Owing to the unsettled conditions

in Italy their work has been interrupted. The value of their findings is difficult to estimate. With no personal experience I am very skeptical as to the organisms and as to the results believed to have been obtained from the vaccine. It is possible that the visible tiny organisms allow the measles virus to develop.

We now come to an extremely interesting subject. The possibility that measles not only may be due to a filterable virus, but that this may have been grown in symbiosis with another microörganism.

In November, 1925, Degkwitz (5), after long experimentation reported that he had cultivated the virus of measles and had produced in animals an antimeasles serum which could be used in man both as a preventive and as a therapeutic agent. He was able in a suitably buffered serum medium to get a development of a filterable virus in symbiosis with other microörganisms. He was able to transfer the living virus with the culture material successfully to a second flask, from that to a third, etc., up to 15 transverse with continued development. A smaller amount of this fifteenth transfer culture would infect monkeys and human volunteers than was required to produce infection from the original blood or nasal secretion. The virus, when kept cool in the ice-box, remained alive for four to five weeks. This culture material did not contain any visible microörganisms and was filterable.

He is now in this country, for a time, working with Drs. McCoy and Harrison in the Hygienic Laboratory. He has already produced what they consider to be measles in monkeys with the transfer of the virus in culture material. He is gathering strains of virus from different cases. One of the large biologial plants is preparing the antiserum in goats, since it is believed unwise to use horse serum for preventive inoculations as widely as it is hoped to use this. The serum is protected by a patent, as is apparently to become the frequent even if undesirable practice. Only a few reports of the results of its use have been given.

Degkwitz first hoped to develop a vaccine, but found the dead virus would not produce immunity and that if he vaccinated with the virus from the culture he could not judge the virulence of the material and the children sometimes develop severe measles. He, therefore, turned to the attempt to develop immunizing and therapeutic anti-

bodies in animals. In this endeavor he believes he has been successful. He found that when the serum was given as a preventive immediately after exposure that it was worthless, but when given between the seventh and eleventh day after exposure, it sometimes aborted the disease or more generally greatly lessened its severity. The best time to use the serum is on about the eleventh day after the exposure when the temperature begins to rise. The dose is 5 to 10 cc. according to the potency of the serum and the size of the individual. For treatment in the early stages of the disease 30 cc. is given to children under four years of age.

Degkwitz believes that the reason the serum is ineffective when given at the time of exposure or shortly afterwards is because it is from the goat or sheep. It is well known that foreign antibodies are retained but a few days in the human body. This idea is reasonable to a certain degree, but it would seem that the antibodies, if potent, should at least restrain the development of the measles virus and so prolong the period of incubation for a number of days.

The favorable results reported by Degkwitz have not been wholly corroborated by others.

Kochman, in the *Deutsche med. Woch.*, 2 April, 1926, reports the results of the attempt to prevent an outbeak of measles in a children's ward of a hospital by means of the serum of Degkwitz. It failed completely. Of the 19 exposed and injected, only 6 remained exempt, and each of these had a reason such as a probable history of measles, the leaving of the hospital before the time was up, etc. Two of the injected children died from their attacks. Their autopsy revealed no lesions sufficient to account for death except those due to the measles or its complications. Of the other 11 measles cases, 5 ran a normal course. The remaining 6 had severe complications. The requirement that the serum should be given on the seventh to eleventh day of exposure is usually impossible to carry out, because of the difficulty of determining this. In the series one case developed measles four days after the injection and yet had it severely and died from it. The statement of Degkwitz that larger doses given during the prodromal stages would modify the attack has not been sufficiently tested. The dose of 30 cc. in small children is fairly large, and may be of some harm in causing in a moderate percentage severe serum sickness.

Degkwitz has left with me a quantity of goat serum, and just as soon as I have an opportunity I expect to test its value. The statements of Degkwitz are so definite and the idea of symbiotic growth is so interesting and plausible that I hope further work will confirm the correctness of his findings. As to the preventive and therapeutic value of his serum it is, I think, too early to form a judgment.

Convalescent human serum. This is the most reliable and least deleterious preventive that we have at present As the work that I did on this subject was published last June in an article by Freeman and myself I know you will excuse me if I quote from it (6).

The first results published on the use of convalescent measles serum were by Nicolle and Conseil. In the same year, 1916, Park and Zingher injected forty-one very recently exposed children at the Metropolitan Hospital. Twenty of these children received 8 cc. of serum, and none of them developed measles. Twenty-one received 4 cc. and three developed the disease, one on the fifteenth day, one the seventeenth day and one on the twenty-fifth day after the serum was given.

Since then, a number of articles have been published on the use of whole blood, serum and plasma obtained from measles convalescents (7). Degkwitz, in 1920, 1921 and 1922, published the results obtained by him and those working with him in more than 1000 cases. The results were on the whole quite favorable in that if the disease was not prevented in some, it was lessened in its severity. His routine method was to draw the blood between the seventh and seventeenth day after convalescence, allow it to clot, and to use the serum intramuscularly after sterility and Wassermann tests had been done. Degkwitz does not believe that the results obtained warrant the use of serum after the seventh day of exposure. He reports among his own series 85 per cent complete protection. This is more favorable than the results in other large series. Probably some of his children were not very markedly exposed.

Amounts of serum used by Degkwitz

2.5 cc. in those exposed 4 days or less
5.0 cc. in those exposed 6 days or less
7.0 cc. in those exposed 7 days or less

Since 1921, the convalescent serum has been utilized with excellent results in the hospitals for contagious diseases in New York City in children who have been exposed by the development of measles in the wards. A grant of money by the Metropolitan Life Insurance Company made it possible to attempt to provide enough serum for all exposed inmates in children's institutions in New York City, and also for all the children in the city who were under three. These classes of children were chosen because institutional children and those under three years of age are the most liable to pneumonia.

The use of convalescent serum in an infected child may prevent the development of the disease, modify the severity of the attack, or fail entirely of any effect. So far as the interests of the child are concerned, the best result is the development of a very mild attack. Under such conditions there is practically no danger of complicating pneumonia or any other complication. Recovery is practically certain, and the child has the advantage of an active immunity which may be considered lifelong. Those children have as a rule a very slight rise of temperature, perhaps to 100° or 101° for a day or so, and a slight coryza and a very slight to a moderate rash. Koplik spots may or may not be present. Those who are absolutely protected have only a passive immunity so long as sufficient serum remains, and this varies from about two to four weeks, and depends on the individual and the amount of serum injected. The child is after this period as susceptible as before.

The great problem in the prevention of measles by this method has been the difficulty of obtaining a continuous supply of blood large enough to meet the demands of a big city. When the work was started in New York, as far as possible, every adult measles convalescent was asked to give some blood, for which service a suitable reward was offered. Because of the small incidence of measles in adults in New York City and the usual refusal of patients to give their blood, this source of supply proved to be inadequate. It then came to the attention of the department that there was an epidemic of measles of considerable extent among the young adult students of a Southern university, all of whom came from rural districts. The students volunteered in large numbers to give their blood, and as they had all been treated in the university hospital, the diagnosis of measles was certain.

The method of drawing the blood was as follows: At the Willard Parker Hospital, blood was drawn on the ninth day after the defervescence of fever up to the twenty-first day, but at the Southern university the time was more varied, and some was drawn as late as five months after the disease. In the case of adults, all the blood was drawn through a 16 gauge Luer needle into a 500 cc. bottle containing 20 cc. of 25 per cent sodium citrate solution and 0.3 gram of oxyquinolin sulphate (chinosol) as a preservative. This preparation was used because it was found that in the dilution in which it was used it was an efficient bactericidal agent; the red cells were not destroyed, and it was not irritating when injected intramuscularly. The bottles were then put in the icebox and the cells allowed to settle,

TABLE 8

Data in institutional children receiving preventive injections

AMOUNT OF PLASMA INJECTED	NUMBER OF CHILDREN	MODIFIED MEASLES	UNMODIFIED MEASLES	COMPLETE SUCCESS	COMPLETE AND INCOMPLETE SUCCESS
		per cent	*per cent*	*per cent*	*per cent*
3 cc.	219	20	8	72	92
4 and 5 cc.	190	8	2	90	98
6 to 10 cc.	243	6	2	92	98
Total in institutions.	753	11	5	84	95
Total in families.	226	42	5	52	95

or were centrifugalized, and the plasma pipetted off. Blood for a Wassermann test was taken at the time of bleeding, and a sterility test was done at the time the plasma was put up into small bottles.

Plasma was used instead of serum, because of the greater yield for the amount of blood drawn and the greater ease of handling. All the blood drawn within six days of the same period in convalescence was pooled. Thus far, the figures indicate that the efficiency of the plasma is not markedly diminished by postponing bleedings for three months after the occurrence of the disease, and that storage in the icebox for six months does not appreciably alter its usefulness. The plasma was put up in 3 cc. and 6 cc. vials and 30 cc. bottles. The vials were distributed to private physicians with printed directions

for use, and a card was given which was filled out by the physician and mailed back to the laboratory. This card contains questions concerning the number of children exposed, the date and type of exposure, the date of injection, and the lot number of plasma. Twenty-one days after injection, the case was investigated by a member of the department staff. The 30 cc. bottles were kept for institutional use when a large number of children were to be injected.

Results obtained in New York City. More than 1500 children received preventive injections between December 1, 1924, and June 1, 1926. From 979, we have fairly accurate data as to the date and degree of exposure, the amount of plasma injected, and the success attained.

Of these 979 children, 753 were exposed in institutions and 226 in private families. In 404 of the institutional children and in all of the children in families, the exposure was direct. In 349 it was indirect, in that actual personal contact with a measles patient was not proved.

No bad effect followed the injections in any case. Only one of the children died, and this one had an empyema before contracting modified measles and was only two years of age. We do not think that the attack of measles appreciably hastened its death.

CONCLUSIONS

We drew the following conclusions as to the value of convalescent blood:

The injection of 6 cc. of convalescent serum or plasma into a child under three years of age and from 6 to 10 cc. for a child over that age who has been exposed for less than five days to measles is sufficient, as a rule, to prevent infection. If it does not, it almost certainly so modifies the attack that it is very mild and is not likely to lead to complications.

The prompt use of the serum will prevent serious outbreaks of measles from developing in institutions and so prevent the development of complicating pneumonias.

It would be of extreme value to have a supply on hand to prevent outbreaks of measles among troops, such as occurred so disastrously in the late war.

The serum gives immunity for only two weeks to one month. In the modified cases there is lasting immunity.

The serum gives the greatest accumulation of antibody shortly after the convalescence of the patient. At the end of three months, the antibodies are still abundant but probably less in amount.

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THE PREPARATION AND USE OF SCARLATINAL ANTITOXIN[1,2]

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That *Streptococcus scarlatinae*, a type of hemolytic streptococcus, is the sole causative agent of scarlet fever is believed at the present time by a large number of students of this disease. The acceptance of the etiological significance of the streptococcus depends upon a large series of very convincing observations. The existence of a filter passing virus specifically related to scarlatina, an assumed etiology accepted for many years, has never been demonstrated with sufficient clearness to carry conviction. The belief so generally held at one time that the etiological agent of scarlet fever is an ultramicroscopic virus developed rather from the failure to discover an acceptible organism of known characteristics than from any very positive evidence in favor of a filterable organism. On the other hand, during the long period of time that scarlet fever has been studied, a greater and greater number of significant facts pointing to the etiological relationship of streptococcus to this disease have been discovered. At a very early period the frequent presence of hemolytic streptococcus in the throats of scarlet fever patients, and occasional invasion of the blood by this organism was observed. As more careful bacteriological studies came to be made, proof was obtained that *S. hemolyticus* is present in predominating numbers during the first days of the disease in the throat of every individual suffering from scarlet fever. Immunological studies of the organisms obtained indicate that they have a certain degree of serologic specificity. Accidental infection by *Streptococcus scarlatinae* of at least one human being with the subsequent development of scarlet fever has been reported. Experimental production of a disease in animals resembling scarlet fever and associated with the presence of *S. scarlatinae* has also been observed.

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In 1923, Dick and Dick caused experimental scarlet fever in human volunteers by inoculation of the throat with a pure culture of *S. scarlatinae* obtained from a patient suffering from scarlet fever. These observers have also produced the rash of scarlatina and certain other symptoms by injecting human beings with a bacteria-free filtrate of a pure culture of the hemolytic streptococcus of scarlet fever. These phenomena do not develop in immune individuals. Nicolle and his co-workers have confirmed the experimental production of scarlet fever in human beings by means of *S. scarlatinae.* Very early in the more exact bacteriological study of scarlet fever, Gabritschewsky and his assistants demonstrated that most of the clinical manifestations of scarlet fever could be reproduced in human beings by inoculation with a broth vaccine made from the hemolytic streptococcus of scarlet fever. This vaccine was used for purposes of specific prophylaxis and seemed to diminish the incidence of the disease in epidemic areas. In 1924, Dochez and Sherman prepared an antiserum by the immunization of horses to *S. scarlatinae*, which possessed the capacity, when injected intracutaneously in a scarlet fever patient during the height of the rash, to blanch the rash specifically about the area of inoculation. This serum was shown by Blake, Trask and Lynch to have the power of curing rapidly the toxic phase of scarlet fever when given intramuscularly in sufficient quantities. The studies briefly detailed have led to the acceptance of *S. scarlatinae* as the etiological agent of scarlet fever and have given rise to a more comprehensive understanding of the pathological and clinical phenomena of this disease.

The site of initiation of infection in scarlet fever is in most instances the throat. Wounds, burns and occasionally the puerperal uterus may serve as the primary focus of infection. Once *Streptococcus scarlatinae* becomes established, it begins to elaborate a toxic substance which readily passes into the blood much after the manner of the toxin of *B. diphtheriae.* In its simplest form, therefore, scarlet fever is a local infection of the superficial tissues of the throat with streptococcus. Like most streptococcus infections, the incubation period of the disease is short. With the spread of infection, increasing amounts of the toxic substance are absorbed and give rise to the clinical manifestations of the disease. The most conspicuous

feature of scarlatina is the rash, which may vary from a slight punctiform erythema to a boiled lobster red rash of uniform intensity over the whole body. In extremely severe instances of the disease, the rash may be hemorrhagic. The rash is now generally believed to be due to the circulation of a toxic substance which sets up in the blood vessels of the skin an inflammatory process which is accompanied by a certain amount of exudation. That such a toxic substance actually circulates in the blood has been conclusively proven by Blake and Trask who have observed that throughout the toxic phase of the disease there is present in the blood and urine a substance which, when injected into the skin of a normal susceptible individual, induces within a few hours the development of a local area of erythema resembling the rash of scarlet fever. The rash producing effect of this substance can readily be neutralized by convalescent scarlatinal serum or by a scarlatinal antitoxin produced artificially in horses. Preceding and accompanying the development of the rash in scarlet fever are certain other toxic manifestations such as nausea, vomiting, high fever, rapid pulse, prostration and delirium. The toxic period in the average case lasts from four to seven days. At the end of this time, the body begins to form antitoxin in increasing amounts, the circulating toxin is neutralized and there appears a predominance of antitoxin in the blood. When no complications have developed, this phenomenon leads to a disappearance of the rash and other toxic symptoms, and a healing of the local lesion in the throat so that the acute phase of the disease is terminated. Unlike the diphtheria bacillus in diphtheria, *Streptococcus scarlatinae* manifests a marked tendency to invade the tissues locally, to extend to adjacent structures and organs, and even to penetrate the blood and establish metastatic foci in distant parts of the body. For this reason, superimposed on the specific toxemia of scarlet fever in an increasing proportion of cases as the disease progresses, are the septic aspects, due to extension of the infectious process. Septic manifestations may appear in the first days of scarlet fever, but more frequently do not become obvious until the rash has been present for several days for even as late as the period of fading exanthem. The septic phase manifests itself clinically as a purulent rhino-pharyngitis, sinusitis, otitis media, mastoiditis, cervical adenitis, cellulitis, thrombo-phlebitis, and septicemia. By

the end of the first week these septic processes have in many instances become the most important factors in the continuance of the disease. Even when such a course of events takes place and the septic complications become more severe adequate antitoxin formation may occur, as is proved by the disappearance of circulating toxin from the blood and the fading of the rash. The specific toxemia of scarlet fever may, therefore, be eliminated at a time when the septic process is continuing to develop and to become more severe.

During convalescence from scarlet fever, in a certain proportion of instances, sequelae of varying character appear. The most important of these are acute nephritis, non-suppurative arthritis, the so-called scarlatinal rheumatism, endocarditis, and inflammation of the serous surfaces of the pericardium and pleura. The relationship and significance of these processes in the course of scarlet fever is not understood at the present time. In any consideration of the treatment of scarlet fever with antitoxin it is important that the three phases of the disease described should be kept clearly in mind.

Investigators of scarlet fever have been for many years impressed with the possibility of the importance of a toxic substance in this disease, similar in its action to the toxin of diphtheria bacillus. Bergé, as early as 1895, suggested that scarlatina is due to a local infection of the throat with streptococcus and that the general symptoms of the disease are caused, as in diphtheria, by the absorption into the circulation of soluble toxins, formed by the infecting microorganism at the site of the local disease. Gabritschewsky and his co-workers, in their studies of scarlatiniform manifestations which followed immunization of human beings against scarlet fever by means of killed cultures of *Streptococcus scarlatinae*, attributed these reactions to the presence of a toxin in the vaccine. They drew attention to the absence of a vaccine erythema in individuals who gave a history of having had scarlet fever, and its failure to develop in patients during the period of convalescence from this disease. Savchenko later was able to demonstrate the presence of a soluble toxin in filtrates of streptococcus, obtained from various localities, in patients suffering from scarlet fever. By immunization of horses to this toxin, an antitoxin was prepared which was used with favorable results in the treatment of human scarlet fever by Menshikov. By

such methods of standardization as were available, the antitoxin was shown to be equivalent to or perhaps slightly more potent than Moser's serum.

Much evidence in favor of a soluble circulating poison in scarlet fever has also come from the study of the Schultz-Charlton extinction phenomenon. In 1918, Schultz and Charlton discovered that if one injects into the skin of a scarlet fever patient, with a bright red rash, 1 cc. of serum from certain normal persons or from a patient convalescent from scarlet fever, there appears, at the site of injection, after about six hours a complete blanching of the rash over an area of from one-half inch to a few inches in diameter. On the other hand, serums taken from scarlet fever patients during the acute stage of the illness invariably gave negative results. Subsequent investigators abundantly corroborated the accuracy of the observations of Schultz and Charlton. The Schultz-Charlton reaction was first used as a diagnostic test of scarlet fever, and the capacity to extinguish the rash was believed to be due to a normal property of human serum, which is temporarily lost during the acute stage of scarlet fever and regained during convalescence. In 1923, Mair published a study of the Schultz-Charlton reaction in which he confirmed in general the observations of the previous workers, but gave the phenomenon a much more satisfactory explanation. He had an opportunity of studying the blanching power of the serum of a child, both before and after an attack of scarlet fever, and showed that the serum before the attack gave a negative Schultz-Charlton test, but during convalescence acquired the capacity to extinguish an active rash. This disproved the previous belief that a positive reaction was due to some property of normal human serum which is lost during the acute stages of scarlet fever. Mair had been interested for some years in the resemblance of scarlet fever to diphtheria. As a result of the observation described and other work, he came to believe that the rash and other changes in the skin in scarlet fever are due to a scarlatinal toxin which has entered into combination with the tissue cells. He supposes that the serum giving a positive Schultz-Charlton reaction contains an antitoxin which is able to dislodge and neutralize the toxin fixed in the cells, and thus restore their normal function over the area injected. He also adds that when the causal organism

of scarlet fever is discovered, it should be capable of producing a toxin, and that the immunization of animals to this toxin should give rise to an antitoxin capable of producing a positive Schultz-Charlton reaction in man.

At the time of the publication of Mair's observations, I had already produced in horses by immunization to *S. scarlatinae*, an antitoxic serum of the type postulated by him. Because of the fact that occasionally, in guinea pigs inoculated for the purpose of producing experimental scarlet fever, enough poison is absorbed from a strictly local lesion to kill the animals, similar local injections were made use of for the production of an antitoxic serum in horses. After nine months a serum was obtained which corresponded qualitatively with human convalescent serum, but which was far more potent in its antitoxic activity. When injected intracutaneously in a patient with a bright red rash, in the acute stage of scarlet fever, this serum caused a complete extinction of the rash over an area five to ten centimeters in diameter. The blanching appeared in from six to twelve hours following injection of the serum and persisted throughout the course of the disease. As a rule, the characteristic pigmentation and desquamation were absent during convalescence over the blanched area. Furthermore, scarlatiniform rashes in such conditions as erysipelas, measles and other exanthematic conditions were not influenced by the intracutaneous injection of the scarlatinal antitoxin. Dick and Dick, in their further studies in 1924, demonstrated the presence of a toxic substance in filtrates of a broth culture of *S. scarlatinae*. The toxic filtrate was obtained from a strain of streptococcus with which these authors had produced experimental scarlet fever in man. When susceptible individuals were injected intracutaneously with small amounts of this toxin, within a certain number of hours, there appeared at the site of inoculation, a circular area of erythema, and occasionally swelling, which increased in size for about twenty-four hours. Patients who have previously had scarlet fever, or those who are convalescing from the disease, in general, react negatively to such intracutaneous injections. When larger doses are administered to susceptible persons, certain of the toxic manifestations of scarlet fever, such as nausea, vomiting, fever and a general erythematous rash are induced. The activity of this toxic filtrate

is readily neutralized by convalescent scarlatinal serum. These studies indicate that sterile filtrates of *S. scarlatinae* contain a toxic substance bearing a specific relationship to scarlet fever. This information, added to the knowledge of the character of the action of an antiserum prepared by the immunization of horses to the same organism, throws great light upon the nature of intoxication and immunity in scarlet fever.

Antistreptococcic serum, prepared by various methods, has been used in the treatment of scarlet fever for many years. In 1895, Marmorek immunized animals to a group of strains of streptococcus derived from different sources. The viruence of the organisms was maintained at a high level by passage through mice and rabbits. The polyvalent serum developed in this way was used in the treatment of a number of streptococcus infections, including scarlet fever. The therapeutic results obtained by the employment of Marmorek's serum in the treatment of scarlatina were disappointing to a number of observers and its use was soon abandoned. Some years later, in 1903, Moser prepared an antistreptococcic serum for use in scarlet fever by the immunization of horses to strains of *Streptococcus hemolyticus* isolated from the blood of fatal and malignant cases of scarlet fever. The organisms were not passed through animals for fear of altering in some way their biological characteristics. Moser's serum received an extensive therapeutic trial in Central Europe and Russia. The results reported from its use were generally favorable, especially those of Schick. Its action seemed to be largely antitoxic in character, and in the individual case of scarlet fever caused a marked drop in temperature and pulse, a diminution of the toxemia, early disappearance of the rash with some local blanching about the area of injection, and a considerable shortening of the duration of the disease. Escherich is reported to have likened its action to diphtheria antitoxin. Moser's serum was used with some success for a number of years in Vienna, but its use was finally discontinued because of the disappearance of the severe type of scarlet fever and the severity of the serum disease which it caused owing to the large doses, 150 to 200 cc., necessary to obtain satisfactory results. Gabritschewsky observed that Moser's serum, when given prophylactically, prevented the development of vaccine erythema in individuals who were under-

going immunization with the streptococcus of scarlet fever. Because of the continued severity of scarlet fever in Russia, Moser's serum remained popular there for many years, and Aksenov reported as late at 1921 the treatment of a large number of cases with distinctly beneficial results. Nicol in the United States, also used in a limited number of instances, antistreptococcus serum in the treatment of scarlet fever. However, because of the growing disbelief in the etiological significance of streptococcus in this disease, the therapeutic use of antistreptococcic serum was practically given up.

As a result of the studies of the streptococcus of scarlet fever, which were again undertaken in 1920 and which succeeded a few years later in proving the specific relationship of this organism to the disease, interest in the therapeutic possibilities of an antiserum prepared from *S. scarlatinae* was revived. We had been studying the relationship of *S. hemolyticus* to scarlet fever for a number of years, and had come to the conclusion, from a consideration of previous work and from certain serological and epidemiological investigations, that this organism was the probable causative agent of the disease. It also seemed to us that in certain respects scarlatina bears a very close analogy to diphtheria in that it is essentially a local infection and that the symptomatology is dependent upon the absorption of a toxic substance from the local lesion. We had tried to produce experimental scarlet fever in animals with streptococcus, but had failed, largely because of our inability to produce and maintain a local lesion which would serve as a focus of infection from which absorption might take place. In order to achieve the latter result, we finally hit upon the expedient of injecting a small mass of fluid nutrient agar beneath the skin and subsequently infecting this material with a typical strain of *S. scarlatinae*. With proper dosage the local focus remained actively infected for a number of days, and there was no invasion of the blood stream or serous cavities of the body by the streptococcus. In this way a syndrome resembling scarlet fever in certain of its aspects was produced in guinea pigs. A certain number of animals so inoculated died acutely without marked spread of the local infection. This indicated the absorption of a sufficient quantity of the toxic subsance from the local focus to bring about a fatal toxemia. Our goal at this time was to produce an antitoxic serum in animals

which would give a positive Schultz-Charlton extinction phenomenon. We had previously tried to produce such a serum in rabbits by the use of whole broth cultures, but had not met with success. In view, therefore, of the absorption of such large amounts of toxin from an infected agar focus we decided to attempt the immunization of horses by this procedure as the one most certain to produce the antitoxin serum which we were seeking. The horse was injected subcutaneously with from 10 to 20 cc. of melted nutrient agar. Within five to ten minutes this mass lying directly beneath the skin, was infiltrated with an initial dose of 20 cc. of living streptococci, taken up in a small volume of broth. This inoculation resulted in the formation of a local abscess, and marked general reaction on the part of the horse. Similar injections were repeated every three weeks, increasing the dose of streptococcus slowly from the residue of 20 cc. of broth culture up to the residue from 400 cc. of broth culture. After a series of such injections, extending over a period of nine months, the animal was bled and his serum tested for its specific effect upon scarlet fever.

An experimental study of the antitoxic value of this serum was undertaken by Blake, Trask and Lynch. These investigators demonstrated its antitoxic action by showing that intracutaneous injection of the serum in patients with scarlet fever causes a local blanching of the rash (Schultz-Charlton rash extinction phenomenon) at the site of the injection, thus indicating the presence of antitoxin in the serum, and its ability to neutralize toxin in the tissues. The antitoxin also neutralizes, *in vitro*, the specific toxin which has been demonstrated by Blake and Trask to be present in the blood of patients during the exanthematous stage of scarlet fever. Moreover, when the antitoxin is administered to patients in adequate therapeutic dosage, the specific toxin present in the blood disappears, a fact which shows the capacity of the antitoxin to neutralize, *in vivo*, the circulating toxin in patients acutely ill with scarlet fever. Simultaneously with the disappearance of the toxin from the patient's blood, the patient's serum acquires the power to produce a positive Schultz-Charlton rash extinction test, which shows that adequate therapeutic dosage not only neutralizes the toxin, but promptly establishes an excess of antitoxin in the patient's blood (fig. 1). They also observed that the treatment of uncomplicated toxic cases of scarlet fever

with this scarlatinal antitoxin results in a critical cure of the disease. In combined toxic and septic cases it similarly neutralizes the specific toxic effects of the disease, but benefits the septic aspects only indirectly by curing the toxemia. They found in post-scarlatinal sepsis after the specific toxic phase has terminated, that the antitoxin exerts no demonstratable therapeutic effect. The therapeutic value and other antitoxin qualities of the serum were later corroborated by Birkhaug, Park, Thenebe, Robb, Friedemann and others. The

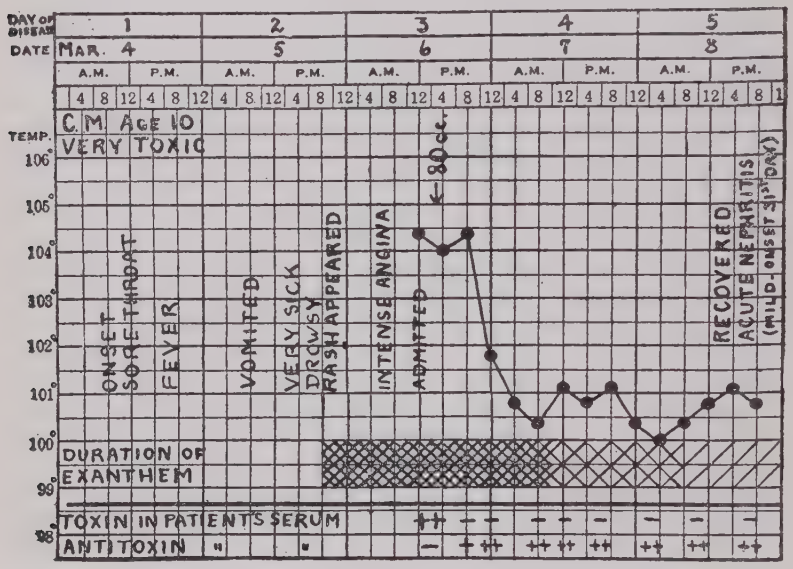

Fig. 1. Analysis of effect of treatment of scarlet fever with scarlatinal streptococcus antitoxin (Blake and Trask).

therapeutic efficiency of the serum seems to depend principally upon its antitoxin content. Antibacterial bodies of the ordinary variety are also present, but whether these have an effect of any importance upon the course of infection in scarlet fever has not been determined at the present time.

Dick and Dick have prepared a scarlatinal antitoxin by the immunization of horses to the toxin obtained by passing broth or blood broth cultures of *S. scarlatinae* through a Berkefeld filter. The filtrate is thus freed from living organisms and contains the same toxic

substances which these investigators had proven to bear a specific relationship to immunity in scarlet fever. The technique of producing scarlatinal antitoxin in large quantities according to the Dick method, has been described by Anderson and Leonard. The medium used for the production of the toxin is a horse meat broth containing 1 per cent peptone, 0.5 per cent sodium chloride, and 1 per cent citrated horse blood, and is brought to a final pH value of 7.5 and 7.8. The culture in this medium is incubated for five days, at the end of which time 0.5 per cent phenol is added. The mixture is allowed to stand for twenty-four hours after which time it is either passed through a Berkefeld filter or a Sharples centrifuge. After sterility tests have been completed, the toxic content of the filtrate per cubic centimeter is measured in skin test doses, one skin test dose being the minimal amount of toxin required to produce a positive Dick reaction in a susceptible individual. The horses were immunized by repeated injections of the above material, which contained from 20,000 to 100,000 skin test doses per cubic centimeter, using essentially the same technique which is employed in the preparation of diphtheria antitoxin. The initial dosage is 50 cc. of toxin containing at least 20,000 skin test doses per cubic centimeter, and the dose is doubled at each succeeding injection until the animal shows some general reaction. In the beginning, the horses receive three injections weekly, but after the maximum volume is reached, the animals are injected twice weekly. Three months after the beginning of immunization the serum of these horses contains sufficient antitoxin to make it serviceable for therapeutic use. Clinical reports indicating the therapeutic value of scarlatinal antitoxin prepared by this method have been published.

A number of manufacturers of scarlatinal antitoxin have preferred to use some modification of the old Moser method of immunization, using combinations of the bodies of *S. scarlatinae* and the soluble toxic substance. At the present time, therefore, it is produced by a variety of methods, some of which employ filtered toxin, elaborated by *S. scarlatinae* grown *in vitro*, other injections of the living organisms in a particular way, and still other combinations of these two procedures. The use of living organisms is supposed by some to produce a higher antitoxin content in the serum and to endow it with anti-

bacterial qualities which are thought to be of some value in preventing the development or checking the advance of septic processes.

Most of the antitoxin, now in use, has been concentrated by a modification of the Banzhaf method for the concentration of diphtheria antitoxin. Accurate comparisons of the therapeutic value in scarlet fever of unconcentrated and concentrated antitoxin have not yet been published so that the relative efficiency of the two products is unknown. That there is some loss of effective bodies during the process of concentration seems likely, and some observers are again advocating the use of a highly potent whole serum.

The antitoxin content of scarlatinal antiserum may be measured by two methods. One method consists in determining the smallest amount of serum that will produce a positive rash extinction test, by injecting intracutaneously in a patient with scarlet fever a series of increasing dilutions of the serum. The smallest amount giving a positive blanching has been designated by Blake and Trask as the minimal blanching dose. In a series of comparative tests these authors have shown that scarlatinal antitoxin should contain at least 12,500 minimal blanching doses of antitoxin per cubic centimeter of serum in order to be therapeutically efficient in doses of reasonable volume. The other method proposed by Dick and Dick measures antitoxin content in terms of skin test doses actually neutralized in the skin of human beings by selected amounts of antitoxin. This method has been accepted as the standard by the Hygienic Laboratory of the United States Public Health Service, and the minimum requirements for scarlet fever streptococcus antitoxin have been defined. The technique, in brief, consists in determining by a series of comparative mixtures the amount of antitoxin required to neutralize exactly at least five skin test doses of a standard toxin. A double series of tests should be made, one with the serum of unknown antitoxic content and another with standardized antitoxin furnished by the Hygienic Laboratory. Parallel observations should be made in three or more persons, susceptible to the toxin, in order to avoid unreliable conclusions dependent upon individual peculiarities of reactivity. Careful controls of sensitivity of the test subject to horse serum must be made. Individuals who give a reaction to horse serum measuring more than four millimeters in any direction,

or who give a negative reaction to the injection of one skin test dose of the standard toxin are not considered satisfactory for test purposes. The reactions are read at the end of twenty-four hours, and again after forty-eight hours. No antitoxin for the treatment of scarlet fever is permitted to be distributed unless proper tests have shown that 1 cc. will neutralize and hold in neutralizaton for forty-eight hours a minmum of 10,000 skin test doses of the control toxin. A unit for scarlatinal antitoxin has been suggested, the unit being that amount of antitoxin which will just neutralize 100 skin test doses of toxin.

Kirkbride and Wheeler have found that the skin of a certain race of goats is sensitive to scarlatinal toxin, and they have been able to carry out successful neutralization tests for purposes of standardization in the skin of these animals. The technique of the method is in general similar to that employed when human beings are used as test objects.

The dosage of antitoxin is an individual instance of scarlet fever should be sufficient to secure prompt neutralization of toxin and simultaneous establishment of a considerable excess of antitoxin in the circulating blood of the patient as early as possible in the course of the disease. The amount of antitoxin required to accomplish this result varies with the size of the patient, the severity of the disease, and the method of administration. In order to determine the proper dosage as accurately as possible, Blake and Trask have determined the presence of toxin and antitoxin in the blood before and at intervals after treatment in a considerable series of cases of scarlet fever, at different ages and degrees of severity, treated intramuscularly with varying amounts of antitoxin, and correlated the results with the therapeutic effect. On the basis of these studies, they recommend the dosage for intramuscular administration presented in the table on the following page (table 1). The full dose of antitoxin estimated according to the figures in this table should be given at once as soon as the diagnosis of scarlet fever is made. A sufficient single dose given early is far more efficacious than the same amount given in divided doses. The antitoxin should be given intramuscularly or intravenously, never subcutaneously, since, when the latter route is chosen, absorption is too slow to attain rapidly the desired effect.

Intramuscular injection is satisfactory for the majority of cases, and the inoculation is preferably given in the anterior or lateral aspect of the mid-thigh. In extremely severe cases it may be advisable to

TABLE 1

Dosage of antitoxin in scarlet fever (Blake and Trask)

CLINICAL SEVERITY	AGE	ANTITOXIN*	EQUIVALENT VOLUME DOSAGES OF ANTITOXINS OF DIFFERENT POTENCIES	
			Potency: skin test doses of toxin neutralized per cubic centimeter	Dosage
		units		*cc.*
Mild and moderate	Children	3,000–4,000	10,000	30–40
			20,000	15–20
			40,000	7.5–10
Mild and moderate	Adults	4,000	10,000	40
			20,000	20
			40,000	10
Severe	Children	4,000–6,000	10,000	40–60
			20,000	20–30
			40,000	10–15
Severe	Adults	6,000–8,000	10,000	60–80
			20,000	30–40
			40,000	15–20
Extremely severe	Children	6,000–8,000	10,000	60–80
			20,000	30–40
			40,000	15–20
Extremely severe	Adults	8,000–12,000	10,000	80–120
			20,000	40–60
			40,000	20–30

* One unit = the amount of antitoxin required to neutralize 100 skin test doses of toxin.

give antitoxin intravenously, or possibly to combine the intramuscular and intravenous routes. In early uncomplicated toxic cases the clinical indications for a second treatment, because of insufficient dosage, are failure of the temperature to fall and the rash to fade

within twenty-four hours after the initial treatment. In the later stage, when septic complications have already arisen, failure of the rash to fade is the most reliable indication, since the temperature in such instances may remain elevated in spite of the fact that the circulating toxin has been neutralized and an adequate excess of antitoxin established in the patient's blood.

Sufficient experience has now been had with the treatment of scarlet fever with antitoxin to justify certain conclusions. Although a final judgment concerning its power to reduce case fatality rate and to diminish the incidence of complications must await a more prolonged experience, the indications at present are that early administration of antitoxin is effective in both of these respects. The clinical effect on the early favorable uncomplicated case of scarlet fever is very conspicuous. Within twelve to thirty-six hours following the administration of antitoxin, there is a subsidence of the toxic manifestations, the rash usually disappears, leaving behind perhaps a slight mottling, the pulse and temperature drop to normal and there is a marked decrease in the leucocytosis. Desquamation is diminished or absent depending upon the stage at which treatment is given. In the cases treated early there is little or no desquamation while in those treated late, the usual desquamation occurs.

The effect of antitoxin in cases of scarlet fever with septic complications varies with the severity and duration of the septic process. In the early instances, when the specific toxemia still persists, there is a rapid disappearance of the toxic signs, and the septic process may subside quickly or be ameliorated. Accompanying this effect there is a drop in the temperature and pulse rate, with the usual fading of the rash. More or less fever may continue, however, depending on the course of the complication. In post-scarlatinal sepsis, even when due to *Streptococcus scarlatinae*, administration of antitoxin seems to be without beneficial action. One of the most important beneficial activities of scarlatinal antitoxin would be its capacity either to ameliorate or prevent the serious disabling complications of this disease. In order to determine its effectiveness in this regard, experience extending over a number of years will be necessary to arrive at accurate conclusions. Experience up to the present time, although of course very limited, indicates that the

administration of antitoxin, early in the toxic stage of scarlet fever, either prevents the development of complications or in certain instances, at least, lessens their severity.

The effect of treatment with antitoxin on the duration of the period of quarantine has not yet been determined. In this country there has been no relaxation of the quarantine regulation by boards of health as a result of the antitoxin treatment. There are some reports from abroad that the time of hospital detention may be curtailed, but prolonged experience will be necessary to determine this point. It would follow, of course, that if septic complications are materially lessened, the period of infectiousness and duration of quarantine would be greatly reduced for a large number of individuals.

As in other instances in which foreign protein is injected for therapeutic purposes, the use of antitoxin in scarlet fever entails the risk of serum reactions. These serum reactions are of two kinds. The early reaction comes within two hours of the administration of antitoxin, and is characterized sometimes by a chill, usually by increased fever and pulse rate. It is not harmful, varies in intensity in different cases, and is, as a rule, more severe when antitoxin is given intravenously. The late reaction or serum disease, as it is commonly called, develops from four days to two weeks after treatment, and resembles that usually encountered after the injection of foreign serum. There is some feeling that scarlatinal antitoxin produces more severe serum disease than diphtheria antitoxin. This is perhaps explainable on the basis that the technique of purifying diphtheria serum has been more perfectly developed and the fact that in the process of concentration it is not possible to heat scarlatinal antitoxin as highly, so that a certain amount of the detoxifying effect of higher temperature is lost. The unpleasantness of the symptoms of serum disease varies greatly, in some cases being characterized by a mildly annoying skin rash, in others by severe urticarial eruption, fever, pain about the joints and edema of the face. Individuals, hypersensitive to horse proteins, are in danger of acute anaphylactic shock, and very careful inquiry should always be made concerning previous serum injections, and the existence of the various allergic conditions such as hay fever, asthma, urticaria or other allergic skin manifestations. When a suspicion of such exists, a careful test of the skin

with horse serum should always be made. If a positive reaction occurs, careful desensitization should be undertaken when it seems imperative to administer antitoxin. The injection of antitoxin should be at once discontinued upon the appearance of anaphylactic symptoms and appropriate remedies adminstered.

The advisability of the general use of antitoxin for the prophylaxis of scarlet fever, as is the practice in diphtheria, is still under discussion. Its adminstration to an exposed individual appears to give an adequate immunity lasting from three weeks to a month. In certain instances, at the end of this period scarlet fever has developed, probably due to the persistence of *S. scarlatinae* in the throat. If it seems advisable for special reasons to secure immediate protection of an individual against scarlet fever, a prophylactic dose of antitoxin should be given. The relatively low percentage of infection after exposure by contact and the frequency with which serum disease occurs has led some observers not to recommend prophylaxis by antitoxin as a universal procedure. A good custom, therefore, is to make a careful daily inspection of all exposed individuals. At the first appearance of fever or sore throat, a full therapeutic dose of antitoxin is given. This effectively checks the disease and reduces the unpleasant incidence of serum disease. When sporadic cases of scarlet fever appear at frequent intervals in schools, small communities, or other closely associated individuals, the best procedure seems to be to employ the method of active immunization, proposed by Dick and Dick for purposes of prevention. Under these conditions antitoxin is used only when necessary as an immediate defense for a short period of time.

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BOVINE TUBERCULOSIS IN ITS RELATION TO MAN[1]

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For the last thirty years bovine tuberculosis has been a cause of much concern to many people. Its ravages have brought discouragement, and often privation, to many cattle owners and its eradication is costing the public millions of dollars annually. Notwithstanding these important bearings on human activities, the problem of greatest moment which this disease has presented is the determination of the extent of its direct relation to tuberculosis in man. For that reason I have restricted my remarks to that particular phase of the subject.

The prominent position tuberculosis holds as a destroyer of human life makes it a matter of grave concern to all members of society. People now living remember when this disease caused approximately 36 per cent of the deaths among men from the ages of twenty to thirty, and 40 per cent between the ages of thirty and forty-five. It is natural that a disease which demanded such a fearful toll from the youth of our land, and of the world, should have received the large amount of attention that has been given to the study and control of tuberculosis. Since the discovery of its cause, great progress has been made in reducing the number of cases. To that end, every phase of domestic and social life affecting the tuberculosis problem has been exploited. The crux of the entire matter seems to rest in its etiology and the means by which people become infected.

The history of the search for the cause of tuberculosis began centuries ago, but little was found until recent years. In 1846, Klenke insisted that milk of tuberculous cattle was infectious for man. In 1865, Villemin demonstrated that tuberculous tissues from both men and cattle would produce the disease in other animals. From that time until the discovery of the tubercle bacillus by Koch, in 1882,

[1] March 7, 1927.

the literature contains records of many experiences illustrating the difficulties and disappointments that were encountered in establishing the specific cause of this disease.

The bacillus of tuberculosis (*Mycobacterium tuberculosis*) was discovered before the idea of a specific etiology in the form of disease-producing microorganisms had been accepted generally. Methods for determining the properties of bacteria, identifying species and distinguishing varieties among them were in their infancy. The relation, or even the existence, of bacteria of a saprophytic nature that closely resembled the pathogenic species was foreign to the subject. It was natural that the outstanding morphological, cultural, staining and pathogenic properties of the tubercle bacillus, as recorded by Koch, should have been accepted as circumscribing the characters necessary for its identification. As they appeared to be the same in tubercle bacilli from men and from cattle, the assumption that they were identical was quite human. Klenke, a quarter of a century before, had made the assertion that milk from tuberculous cattle was infectious for man, which tended to confirm the opinion reached by the study of the organism. The statements by Villemin (1), Klein (2) and Martin (3), that the etiology of human tuberculosis was different from bovine, did not change or modify the accepted conclusion that mammalian tuberculosis was caused by one and the same organism.

Prior to the discovery of the tubercle bacillus, but after the infectiousness of the disease had been demonstrated, there was wide diversion of opinion as to the mode of infection, especially in the pulmonary form. The common accepted theory was that the etiological factor entered through the respiratory tract. Koch supported this belief in his early work and reaffirmed it in 1901. There were a few workers on tuberculosis who protested against air infection. Chauveau as early as 1868 held that the alimentary canal might be the portal of entry more frequently than the air passages. Woodhead called attention, in 1894, to the evidences of intestinal infection, especially in children. This opinion was held generally in France. Calmette strongly supported it. Further, he maintained that the air passages offered more effective resistance to tubercle bacilli than the intestine and its adjacent glands. von Behring advocated not only the digestive tract as the way through which infection took place, but that it

occurred most frequently in infancy and that the bacilli came from cow's milk. This conclusion, while in harmony with that of Calmette and others, supported the opinion that humans suffered much from bovine tubercle bacilli. His views were not challenged in this country where their acceptance brought bovine tuberculosis, as a health measure, prominently before the people.

In 1894, soon after tuberculin had been discovered, official eradication of bovine tuberculosis was undertaken in the State of Massachusetts where a considerable appropriation was made by the legislature, not only for testing cattle, but also for paying indemnities to the owners. In 1895, New York followed the example and since then approximately every state in the union has taken up the work. In 1917, the federal government, in cooperation with the different states, inaugurated a method of eradication known as "the accredited herd" plan, that has been far more successful in interesting animal owners than any procedure that had been tried previously in this country. The project calls for official testing of all cattle in the United States and repeating the test so long as any animals react, and the destruction of the reactors.[2] After one year has elapsed without a reaction the herd is *accredited*. Subsequently such herds are tested by private practitioners and at the owner's expense. A few years since, the "area" plan was adopted, which means that in the eradication program the testing is restricted to the animals in a given area, such as a township, until they are accredited. The summary of the progress of the accredited herd plan issued by the Federal Bureau of Animal Industry for November, 1926, showed that there were at that time 109,512 herds, containing 1,740,712 animals, that had been accredited; 1,729,691 herds and 16,588,345 animals that were under supervision. It was reported that in 1923 the states and federal government had appropriated approximately $15,000,000 for this work.

Although the opinion prevailed for many years that human and bovine tubercle bacilli were identical, there were a few of the earlier investigators who questioned the accuracy of this view. In his experiments to prove the infectiousness of tuberculosis, Villemin states:

> We must remark that none of our rabbits inoculated with human tubercle have presented a tuberculosis so rapid and generalized as that which we

[2] As a rule they are slaughtered for food under federal or state inspection.

have obtained from material from the cow. At first we were inclined to regard this as fortuitous, but subsequent experiments led us to suppose that the tubercle of the bovine race, inoculated into rabbits, possesses a much greater activity than that obtained from man. It may be supposed, like all virulent matter, that tuberculous matter is the more virulent the more the affinity of the animal supplying the virus and the animal receiving it.

Klein (4) in 1883, pointed out that Koch's work did not clearly establish the identity of human and bovine tuberculosis. He himself had observed differences in form and arrangement of tubercle bacilli found in man and bovine lesions and the relative number of microorganisms contained in each. He found that tuberculosis was not produced when human tuberculous matter, full of tubercle bacilli, was injected into rabbits, while the virus from the cow caused a very high degree of generalized disease. From this and other experiments, Klein concluded that "the tuberculous virus derived from the human subject is not exactly the same as that from tubercles of the cow." Some twelve years later Martin (5) pointed out that "It is evident that in case of tuberculous sputum we are dealing with material which is less infective to calves than bovine tuberculous material."

In 1896, Theobald Smith (6) published the results of his studies of two strains of tubercle bacilli, one of bovine origin and the other from a bear (*Nasua narica*), supposed to have contracted the disease from his keeper. In 1898 (7) he published a detailed account of his experiments with 15 strains of tubercle bacilli, 7 from human sputum, 5 from cattle and one each from the cat, horse and pig. His conclusions were that there exists "a distinctively human, or sputum, and bovine variety of tubercle bacilli." Smith pointed out with great clearness the differences between these two types, which exist in their morphology, cultural characters and virulence, especially for rabbits and calves. In a later publication (8) he showed that they exhibited a decided difference in their action on glycerin in the culture medium.

At the meeting of the Seventh International Tuberculosis Congress in 1901, Koch presented the results of his subsequent studies of the two forms of tubercle bacilli. This report was quite startling in character and because of its being almost, if not entirely, a reversal of his earlier views, it created much interest in the subject. The following is taken from his paper.

In view of all these facts, I believe that I am justified in maintaining that human and bovine tuberculosis are not identical and that the human variety can be transmitted to cattle. . . . . But how about the susceptibility of human beings to bovine tuberculosis? These questions cannot be answered directly since, of course, experiments on human beings are not permissible, but we can get at a solution indirectly. It is a well known fact that much of the butter and milk consumed in large cities contains a considerable number of living tubercle bacilli (Perlsucht bacilli). If these are pathogenic to human beings we ought to find among the inhabitants of large cities, who daily swallow these living, virulent organisms, and thus unconsciously carry out the very experiment which we could not undertake, many cases of tuberculosis that can be traced to food contaminated with tubercle bacillus, especially ought this to be true in children. . . . . In reality it is not so. We can admit infection with tuberculosis through food containing tubercle bacilli only when the intestine is the seat of the first lesion, i.e., in case of primary intestinal tuberculosis. Primary intestinal tuberculosis, however, is extremely rare . . . . and in the few cases reported, it has not been conclusively proved that we are dealing with an infection with bovine tuberculosis. . . . . The chances are equally in favor of its being of the human form. . . . . Today we are able to make a diagnosis. It is necessary merely to isolate the organism from the tuberculous material in pure culture and by inoculation into cattle establish whether it is of the human or bovine variety. . . . . For half a year I have experimented along these lines, but, owing to the scarcity of material, have been able to examine only a few cases. So far results do not indicate the occurrence of bovine tuberculosis in man. . . . . Although the question whether man is susceptible to bovine tuberculosis has not been definitely answered, and probably cannot be immediately answered, we may safely say that if such susceptibility does exist, the infection takes place rarely. I should be inclined to consider the number of cases of tuberculosis caused by milk, butter, or meat of tuberculous cattle not much greater than that of hereditary causes, and I believe, therefore, that no special protective measures are indicated.

Thus the very clear differentiation of the human and bovine types of tubercle bacilli made by Smith was confirmed by Koch, who put strong emphasis on the non-transmissibility of bovine tuberculosis to man. His views were opposed vigorously by those who believed in the identity of the mammalian types. Many researches were inaugurated to confirm the findings of Smith relative to the identity or non-

identity of the bacillus from man and the one from cattle. The results left no doubts that there are decided differences between them and that they can be differentiated the one from the other.

The difference between the two types made it possible to determine whether the lesions in man were caused by bacilli of human or bovine origin. Further the incidence of tuberculosis in man and in cattle would tend at least to show to what extent the bovine disease increased or modified the rate of the disease in man. Thus far a considerable number of cases of human tuberculosis, including all forms of its manifestations, have been studied bacteriologically. Further the death rate in human tuberculosis has been obtained in cities where great precautions against infection from milk have been taken and also in restricted areas, such as counties where the amount of the disease in cattle is large and where few, if any, precautions against milk infection have been enforced. The larger number of studies on the types of tubercle bacilli has been made by workers in the Gesundheitsamt in Berlin, the British Commission on Tuberculosis (human and bovine) and the Research Laboratory of the New York City Board of Health. In addition to these more comprehensive investigations, different workers have studied a large number of human specimens. Their results do not change in any essential particular those obtained by the agencies mentioned.

The appended table, compiled by Park and Krumwiede (9) gives a total of 1,220 examinations that have been made for the identification of the type of tubercle bacilli in cases of tuberculosis in man, grouped according to the age of the patient. In four cases, not included in the table, both human and bovine types were found. It should be stated that a large number of these specimens came from persons in whom the bovine type might be suspected because of the exposure of the individual to such infection. (See table 1.)

Kossel (10) gathered the results of the examination of sputum by 27 investigators which showed that of 832 specimens the human type was present in 826, the bovine in 3, both human and bovine in 2 and an unidentified form in 1. In 1917, Cobbett (11) tabulated the results of the examination of 938 specimens of sputum in which 932 contained the human, 4 the bovine and 2 were mixed. The English Royal Commission (12) examined 108 cases of tuberculosis, exclusive of lupus, in

which the human type appeared in 84, the bovine in 19, and both types in 5 cases.

The bacilli found in skin tuberculosis are interesting. The Royal Commission examined 20 cases of lupus of which 1 was due apparently to a bacillus corresponding exactly to the bovine and 2 to the human type; 8 were caused by bacilli that culturally resembled the

TABLE 1

Types of tubercle bacilli in 1,220 human infections

DIAGNOSIS	ADULTS OF MORE THAN 16 YEARS		CHILDREN FROM 5 TO 16 YEARS		CHILDREN YOUNGER THAN 5 YEARS	
	Human	Bovine	Human	Bovine	Human	Bovine
Pulmonary tuberculosis	644	1	11		23	1
Glandular tuberculosis (axillary or inguinal)	2		4		2	
Cervical gland tuberculosis	27	1	36	21	15	21
Abdominal tuberculosis	14	4	8	7	9	13
Generalized tuberculosis (alimentary origin)	6	1	2	3	13	12
Generalized tuberculosis (with meningitis, alimentary origin)	29		5	1	46	13
Generalized tuberculosis (with meningitis)	5		7		52	1
Tuberculous meningitis	1		3		27	4
Bone and joint tuberculosis	27	1	38	3	26	
Genito-urinary tuberculosis	17	1	2			
Cutaneous tuberculosis	3		1		1	
Other tuberculoses: Of the tonsils				1		
Of the mouth and glands of the neck		1				
Of the maxillary sinus	2					
Latent tuberculosis					1	
Total	777	10	117	36	215	65

bovine type, but had a modified virulence for cattle and rabbits; 9 strains resembled the human type, but possessed a lower virulence for monkeys and guinea pigs. Griffith (13) reported a study of 25 cases of the skin form of tuberculosis from which the human type was found in 13, and those resembling more closely the bovine in 12. Rothe and Bierotte (14) examined 28 cases of skin tuberculosis from which they recognized the human type of bacilli in 23, the bovine in 4 and both forms in 1.

The Commission and Laboratories mentioned report a total of 121 cases of tuberculous meningitis that have been studied. Twenty-one were in persons from five to sixteen years of age, from which the human type was isolated in 19 and the bovine in 2. The remaining 100 were in children under five years of age, of which 80 contained the human and 20 the bovine bacilli.

Cobbett collected the reports of the examinations of 57 cases of abdominal tuberculosis, of which 10 were adults. From these the human type was recovered in 8, and both forms were present in 2. In the 47 cases under sixteen years of age, 19 were due apparently to the human type and 28 to the bovine.

The examinations that have been reported of tuberculous bronchial glands show that of the 18 cases, 17 contained the human and one the bovine type of tubercle bacilli. The examination of 49 cervical glands that had been removed surgically from adults showed that 40 contained the human and 9 the bovine organism. The study of 115 such cases in children between the ages of five and sixteen, showed 52 to contain the human and 63 the bovine, and in 83 cases in children under five years of age, 17 showed the human and 68 the bovine type.

According to Cobbett (11) the prevalence of the bovine type in cervical glands that had been removed surgically from persons sixteen years of age and younger, varied considerably in the different countries. In Scotland it was 87 per cent, in the United States 53 per cent, in England 50 per cent, and in Germany 35 per cent.

The analyses of the results of the bacteriological examinations of tuberculous human tissues indicate that in adults the bovine type of tubercle bacilli is exceedingly rare, but in children under five years of age, it is the cause of considerable infection. It is of interest to note that tuberculosis in children apears more often in the glandular form and that the mortality in such cases is lower than in the other manifestations. Likewise it is well to keep in mind the significant fact that while cases of infection with bovine bacilli in children do occur, it is clear that there is no form of human tuberculosis that depends for its existence on this disease in cattle. It is reported that human tuberculosis, including all forms of its manifestation, prevails in countries such as Japan, India, Greenland and others, where cattle are few and where children are not fed cow's milk. In the United States and

Europe the number of cases of glandular tuberculosis in children is influenced to some extent by the bovine disease. The probable source of infection is through raw milk from cows affected with tuberculous udders.

The number of tubercle bacilli necessary to cause infection is important. While the possibility exists that a few virulent bacilli might produce tubercles, the considerable amount of experimental work that has been done on this subject shows that a large number of bacilli are necessary to overcome the usual resistance of experimental animals. Gebhardt was among the first to demonstrate the difference in the number of tubercle bacilli that it requires to produce infection in guinea pigs when administered in different ways. Working with dried sputum, he showed that 800 bacilli would cause infection when taken by inhalation, but 10 to 20 million failed to do so when taken by the mouth. Schroeder and Cotton found that milk which would produce tuberculosis in guinea pigs when 5 cc. was injected into the peritoneal cavity, could be fed thirty days without producing disease. Findel, Reichenback and Alexander (15) found that 400,000,000 tubercle bacilli are necessary to produce infection in guinea pigs when given in a single dose, but that 800,000 given 50 times by mouth was not certain of causing infection. Ostermann (16) reports that milk containing 1000 bacilli per cubic centimeter may be ingested repeatedly without effect. There is no way of determining the susceptibility of young children to this organism. Smith (17) concluded that "bovine tuberculosis may be transmitted to children when the body is overpowered by large numbers of bacilli, as in udder tuberculosis or when certain unknown favorable conditions exist."

The death rate from tuberculosis, as shown in table 2 does not reveal a sudden drop following the introduction of pasteurization of city milk. If the bovine type were the cause of serious infection in man, it would be expected that the destruction of the organisms in market milk would be reflected in a sharp decline in mortality.

It is of interest to note that there has been a reduction in the death rate from tuberculosis in the rural districts, where milk is used in the raw state, corresponding with that in the cities. The danger from milk infection increases with the number of bacilli ingested. In the city supply, the milk that might come from a few cows with tuberculous

udders is diluted by mixing it with a large volume that is uninfected, thereby reducing materially the number of bacilli in any given quan-

TABLE 2

*Tuberculosis mortality among children under fifteen in New York City, 1898 to 1923**

YEAR	MENINGITIS		PULMONARY		ABDOMINAL		OTHER FORMS		ALL FORMS†	
	Deaths	Rate‡	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
1898	786	78	307	31	54	5	223	22	1,370	136
1899	766	74	362	35	40	4	233	23	1,401	136
1900	803	76	316	30	43	4	206	20	1,368	130
1901	675	62	290	26	89	8	137	13	1,191	109
1902	722	64	239	21	78	7	125	11	1,164	103
1903	720	62	259	22	94	8	82	7	1,155	99
1904	663	58	328	28	92	8	95	8	1,178	102
1905	568	48	332	28	75	6	105	9	1,080	91
1906	665	54	350	28	82	7	100	8	1,197	97
1907	664	54	345	28	76	6	88	7	1,173	95
1908	691	54	327	26	86	7	96	7	1,200	94
1909	716	54	364	27	76	6	101	8	1,257	95
1910	688	50	271	20	85	6	155	11	1,199	87
1911	764	55	335	24	74	5	156	11	1,329	95
1912	681	48	287	20	94	7	160	11	1,222	86
1913	694	48	353	25	77	5	164	11	1,288	89
1914	630	43	321	22	65	4	150	10	1,166	79
1915	649	44	324	22	50	3	177	12	1,200	81
1916	568	37	256	17	44	3	135	9	1,003	66
1917	571	37	272	18	42	3	198	13	1,083	71
1918	615	40	314	20	49	3	128	8	1,106	71
1919	479	31	271	17	49	3	115	7	914	58
1920	395	25	241	15	45	3	95	6	776	49
1921	298	18	168	10	32	2	74	5	574	35
1922	320	19	195	12	23	1	82	5	620	37
1923	277	17	162	10	22	1	86	5	547	33

* Compiled from Reports of the New York City Department of Health by G. J. Drolet, Statistician, New York Tuberculosis Association. Bulletin New York Tuberculosis Assoc., Vol. v, No. 5, p. 14.

† Includes acute miliary tuberculosis, Pott's disease, white swelling, scrofula and general tuberculosis.

‡ Death rate per 100,000 children under 15 years of age.

tity. On the contrary, in the country it is consumed as it comes from a single dairy, and often that from a single cow is reserved for the family use. In case such animals have udder tuberculosis, the con-

centration of the bacilli in the milk is so great that only the most resistant can be expected to overcome them. Table 3, kindly furnished me

TABLE 3

Deaths from tuberculosis, pulmonary and all forms, per 100,000 population, New York City and Rest of State, 1900–1925

	PULMONARY		ALL FORMS	
	New York City	Rest of State	New York City	Rest of State
1900	236.5	141.5	279.3	161.5
1901	228.2	144.7	262.3	164.9
1902	205.2	126.7	239.0	143.9
1903	209.7	130.3	241.6	148.5
1904	215.5	139.5	245.1	157.2
1905	208.7	135.1	234.4	155.1
1906	212.0	121.7	239.7	151.8
1907	206.7	219.4	233.7	152.8
1908	197.2	128.8	224.5	151.9
1909	186.5	124.3	212.7	145.7
1910	184.6	124.1	210.5	143.8
1911	184.2	124.9	210.3	142.5
1912	176.8	116.5	201.2	133.5
1913	173.7	115.4	198.7	134.6
1914	178.0	117.9	200.3	135.7
1915	174.3	115.3	196.2	132.2
1916	163.2	114.9	181.6	131.3
1917	168.9	120.2	187.8	137.5
1918	163.5	128.3	184.0	145.1
1919	135.1	111.0	152.4	125.7
1920	111.1	98.9	126.4	112.4
1921	92.1	86.9	104.1	98.9
1922	89.9	84.7	101.1	95.1
1923	88.2	85.4	98.1	95.4
1924	85.5	81.5	95.8	91.3
1925	83.7	79.7	93.1	88.6

by the New York State Health Department, shows that human tuberculosis is declining in the country nearly as fast as it is in the city.

To understand the significance of the data set forth in table 3, the

fact should be kept in mind that while tuberculosis in man is decreasing, it is gradually spreading in cattle, excepting in the areas where intensive eradication work is in operation and in the areas already "cleared." In New York State there were few areas in the milk shed of New York City where all the cattle had been tested and from which the reactors had been removed prior to 1925. In this state

TABLE 4

Deaths from tuberculosis (all forms) and rate per 100,000 population

I. Counties

YEAR	CORTLAND COUNTY		JEFFERSON COUNTY		LEWIS COUNTY		MADISON COUNTY		ONEIDA COUNTY	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
1920	23	77.3	61	73.9	10	42.0	27	68.1	226	122.8
1921	11	36.6	47	56.5	18	75.1	25	62.7	134	71.9
1922	18	59.4	51	60.8	10	41.4	15	37.4	206	109.0
1923	16	52.4	47	55.6	11	45.2	16	39.6	214	111.6
1924	13	42.4	60	70.4	14	57.0	12	29.6	183	94.1
1925	10	32.2	45	52.4	4	16.2	15	36.7	202	102.8

II. Cities

YEAR	BUFFALO		ROCHESTER		SYRACUSE		UTICA		ALBANY	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
1920	534	105.2	221	74.6	118	68.6	78	83.9	164	144.2
1921	554	107.9	190	63.3	122	70.2	52	53.9	137	119.6
1922	510	98.3	149	49.0	84	47.8	63	64.7	131	113.5
1923	538	102.5	185	60.1	101	56.9	73	74.3	134	115.3
1924	529	99.7	183	58.7	82	45.7	62	62.5	130	111.1
1925	470	87.6	176	55.8	84	46.3	63	63.0	137	116.2

intensive work in eradicating bovine tuberculosis was begun in, and for several years was restricted largely to, non-dairying districts, so that its effect on the city milk supply is recent and as yet not extensive. Through the courtesy of Dr. Plunkett of the State Health Department, I obtained the number of deaths due to tuberculosis and the rate per 100,000 of population in several of the counties where the cattle are most heavily infected, and where as yet the animals in but

few townships have been tuberculin tested. In some of these the number of reactors exceeded 50 per cent on the first test, and yet the death rate from human tuberculosis in these same counties declined quite as much as in the state at large. Further, the number of deaths from tuberculosis in the larger cities of the State shows a steady im-

TABLE 5

Mortality from tuberculosis in the State of Illinois and the City of Chicago with death rate per 100,000 population

CALENDAR YEAR		DEATHS	DEATH RATE
1918	Illinois	8,579	135.7
	Chicago	3,820	146.2
1919	Illinois	7,395	114.9
	Chicago	3,246	121.3
1920	Illinois	6,568	100.6
	Chicago	2,658	97.4
1921	Illinois	5,617	84.9
	Chicago	2,362	85.0
1922	Illinois	5,605	83.61
	Chicago	2,220	78.35
1923	Illinois	5,557	81.83
	Chicago	2,335	80.90
1924	Illinois	5,637	82.0
	Chicago	2,434	82.7
1925	Illinois	5,529	79.3
	Chicago	2,489	83.1

provement in the control of this disease. The appended table (table 4) gives the data on these points from 1920 to 1925 inclusive.

In the State of Illinois practically the same condition exists. In January, 1927, only 1,100 herds, containing 31,096 animals, were accredited (tuberculosis free) out of a total of 114,678 herds containing 1,036,971 animals under supervision. With this condition relative to tuberculosis in the cattle there has been a steady decline in the death

rate in human tuberculosis in the state at large as well as in the City of Chicago. The rate in the state dropped from 135.7 in 1918 to 79. 3 in 1925 and in the City of Chicago from 146.2 to 83.1. The data (18) are given in table 5.

The declining death rate in Illinois is attributed to better hospitalization, isolation of advanced cases, instruction of incipient ones in the proper care of themselves and finding, through public health nurses and otherwise, the unknown cases and bringing them under proper treatment. In that state tuberculosis dropped from the top of the list of all causes of death to about sixth place. It can be said for Illinois,

TABLE 6

The number of cattle and swine examined at slaughter by federal meat inspectors and the number of each condemned on account of tuberculosis

YEAR	CATTLE			SWINE		
	Total number	Number condemned	Parts condemned*	Total number	Number condemned	Parts condemned
1900	4,481,000	5,279		23,336,000	5,440	
1907	7,632,098	19,305	10,530	31,823,499	65,618	364,559
1912	7,532,005	35,273	51,576	34,966,378	42,267	314,581
1915	6,965,415	32,644	48,401	36,388,402	66,023	439,915
1920	9,709,819	37,492	54,670	38,848,438	65,609	535,631
1925	9,773,883	61,104	84,027	48,459,608	86,282	939,294

* When tubercles are restricted to a part of a carcass such as the liver or the pleura on one side of the infected organ or part is condemned and the remainder of the carcass is passed. See regulations governing the inspection of meat, U. S. Bureau of Animal Industry, Order 211, Revised, 1926.

as well as for New York, that the improved methods of preventing and treating human tuberculosis has reduced the number of cases in the rural districts quite as much as in the cities. In other words, better methods for preventing and treating human tuberculosis has been effective even where the disease in cattle has been prevalent. I recognize that the data from two states only offers little more than presumptive evidence that tuberculosis in man does not depend, to any appreciable extent, on that disease in cattle.

The rapidity and extent to which tuberculosis has spread among beef cattle and swine in this country since 1900, as determined by the post mortem findings at the time of slaughter, may be gathered from

table 6, compiled from the reports of the Chief of the Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C.

It should be stated that in recent years more dairy cattle than formerly have been slaughtered at official packing plants, which explains some of the increase in condemnations. Tuberculosis is much more prevalent among dairy cattle than in beef animals. The increased amount of tuberculosis in swine is attributed to avian tuberculosis which has become quite extensive in many localities. Van Es and Schalk (19) have found swine tuberculosis to be prevalent in areas from which bovine tuberculosis had been eliminated, but in which swine showed an increased rather than diminished amount of the

TABLE 7

Differentiation of tubercle bacilli by their virulence

BACILLARY TYPE	CAVIA	RABBIT	FOWL
Bovine	+++	+++	0
Human	+++	+	0
Avian	0	+++	+++

+++ = generalized, progressive, fatal tuberculosis; ++ = moderate or conditional virulence; + = slight, non-progressive, local visceral lesions; 0 = absence of visceral lesions.

disease. They have demonstrated that tuberculosis in swine is caused by the avian type of tubercle bacilli.

Some workers have adopted a method of differentiating the human, bovine and avian types of tubercle bacilli by their virulence for rabbits, guinea pigs and fowls which is relatively simple and approximately accurate. The effect of the different types of bacilli on these experimental animals is shown in table 7.

Avian tubercle bacilli have received considerable attention as an etiological factor in tuberculosis of swine and cattle. Eberlin (20) tells us that Gerlach in 1875 transmitted avian tuberculosis to three rabbits and two swine by feeding. O. Bang (21) produced tuberculosis in calves by feeding them cultures of avian tubercle bacilli. Mohler and Washburn (22) found that the microorganisms of naturally acquired tuberculosis of fowls can be made to lodge and multiply within the tis-

sues of swine, cats, rabbits and guinea pigs. They state "repeated passage of such avian tubercle bacilli in large numbers from animal to animal will result in the final development of a type of tubercle bacilli which will produce typical lesions of tuberculosis in mammals."

There is growing evidence that under certain circumstances the avian type of the bacillus may be transmitted to man. Löwenstein (23) identified the avian bacillus in two cases of renal tuberculosis in children and in a cutaneous form with abscesses and ulceration of the nose and intestines. Weber isolated avian bacilli from the feces of a patient suffering with pulmonary tuberculosis. Max Koch and L. Rabinowich (24) cultivated the avian type from the spleen pulp of a man who died of miliary tuberculosis. Perhaps the most conclusive case is that of Jancso and Elfer who obtained it from the mesenteric glands of a girl eight years of age. Lipschütz (25) asserts that avian tubercle bacilli are frequently encountered in certain forms of cutaneous tuberculosis in man.

In a recent address, Van Es (26), of the University of Nebraska, makes this significant statement relative to the avian type. "Definite typing results have convicted the avian strain of tubercle bacilli as the etiological factors in tuberculous infections of man, horse, cattle, swine, rabbits and other mammals. In the case of some of these species the frequency of avian infection is not entirely unknown, and its importance cannot be accurately estimated at this time. In regard to other species, investigational work of recent years has shown that avian tuberculosis does play a part so important as to require the immediate attention of live stock sanitarians." The report of Plum (27) on tuberculosis in cattle, especially in the genital tract, supports the statement by Van Es.

Van Es (26) has studied extensively the types of tubercle bacilli and has presented a table showing the host relations of these organisms, which is exceedingly instructive. It is valuable in suggesting the limitation of hosts outside of the "natural" one in which each of these types may thrive and produce disease.

It is hoped that those who have opportunity of obtaining tuberculous lesions, especially from children, will continue to type the organisms incriminated until sufficient data are obtained to admit of definite conclusions relative to the intercommunicability of the different types.

The theory advanced soon after the differentiation of bovine and human types that the bovine could be changed into the human, and vice versa, received considerable attention. In 1902, von Behring, Römer, and Ruppel (28) reported a strain highly virulent for calves that was obtained through a goat previously inoculated with tubercle bacilli of human origin. Emphasis was placed on the passage of the organism through the goat. Researches on this subject at the Gesundheitsamt by Weber and Huess tended to prove the stability of the two types. Eber of Leipzig (29) was prominent among those who main-

TABLE 8

Host relations of tubercle bacilli

HOST SPECIES	BACILLARY TYPES			
	Bovine	Human	Avian	Atypic
Man	++	+++	+ (*)	(*)
Bovine	+++	0 (*)	+ (*)	(?)
Swine	+++	+ (*)	++	+ (*)
Horse	++	(?)	+ (*)	+ (*)
Sheep	++ (*)	0 (*)	(?)	(?)
Goat	+++	0 (*)	0 (*)	(?)
Cat	++	0 (*)	+ (*)	(?)
Dog	++	++	0 (*)	(?)
Cavia	+++	+++	0	(*)
Rabbit	+++	+	+++	(*)
Fowl	0	0	+++	(*)
Parrot	+++	+++	++	(*)

+++ = full virulence; ++ = moderate or conditional virulence; + = slight virulence; 0 = avirulence; (*) = data insufficient for definite conclusions; (?) = unknown.

tained that human bacilli can be converted into bovine by a sojourn in the ox. He reports a change in the type of human bacilli in 7 of the 31 strains he investigated, but the possibility of substitution was not eliminated entirely. A. S. and F. Grifith made a number of experiments for the Royal Commission with the bovine type on the baboon and chimpanzee, but their results did not show a change of type in the organism used. With a few exceptions, the cultures recovered gave a growth suggestive of the human organism. There is considerable literature on the mutation of types in tubercle bacilli, but, as a rule, the experimental work indicates that they are stable and not changed.

In a few cases where both types have been found in the same individual, the explanation seems to be the existence of mixed infection rather than the modification of the organism. After a type becomes fixed there is little evidence that it changes readily. If the theory is accepted that pathogenesis is acquired gradually by certain acid-fast bacteria under as yet undetermined conditions, it is not illogical to assume that at times there may be a slipping back toward saprophytic properties. This may explain the variation in the virulence of tubercle bacilli that has been reported. While our immediate problem is concerned with cross infection of humans with the bovine type of tubercle bacilli, the larger question is the determination of the agencies that tend to increase the parasitic tendencies of recognized acid-fast bacteria in nature, as determined by their presence in lymphangitis, reported by Traum (30) and the modified forms recorded from skin tuberculosis by many workers.

From the existing knowledge of the principles of bacteriology, the conclusion seems to be justified that in the evolution of tubercle bacilli three distinct types, namely, human, bovine and avian have become established. Each of these has a specific affinity for its respective host, which means that human tuberculosis as a disease of man is due to its particular type of bacillus; that bovine tuberculosis as a disease of cattle is due to its specific type; that avian tuberculosis as a disease of fowls is caused by its type; and that in dealing with these forms of tuberculosis each must be considered as a separate and quite distinct disease.

It appears to be clear that individuals of the different hosts are to a certain degree susceptible to tubercle bacilli of other types, but such cross infection is not transmitted from one individual to another. Further, such infection does not occur unless all the conditions are favorable. Certain species of animals, such as swine and horses, do not appear to have a distinct type of tubercle bacilli, but are quite susceptible to the bovine and avian organisms. In these animals, however, the disease disappears soon after the source of infection is removed. The examinations that have been reported show that humans are, under favorable conditions, susceptible to the bovine type of tubercle bacilli, but for the greater part such infection is in young children where the disease produced is usually localized and glandular.

It does not appear to be the cause of pulmonary disease. In adults such infection is rare, if it occurs at all.

It is believed that most human infection with bovine tubercle bacilli is caused through the ingestion of raw milk from cows with tuberculous udders. The danger can be removed by eradicating the disease in cattle or pasteurizing the milk before it is consumed.

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THE BRITISH COAL MINER

The Personal Factor in Coal Mining[1]

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Coal mining is taken as a subject, because it exhibits in somewhat accentuated forms most of the influences which are intimately concerned with the human factor in industry. These influences, however, are not peculiar to coal mining; they concern human activity of all kinds, and in the interests of economic production, of health, and of that contentment in life which marches *pari passu* with health, they call for far more consideration and attention in modern industry than they have yet received. Economic production should appeal to the entrepreneurs of industry; health of the wage earners reacts on the health of the general community of which they form so large a proportion; contentment means freedom from industrial unrest, than which there is today no greater barrier to the onward progress of civilization.

Coal mining, indeed mining of any sort, is not an occupation with which the human body has through the ages been evolved to cope. Its environment is strange and unfamiliar, due in the main to lack of light and of room to stand upright. Until recently it vied with agriculture in the proportion of energy used which was supplied by human muscle; today agriculture has in this respect left it behind. In no other industry is so much hard physical work done by highly skilled men. This means that the personal factor in this great basic industry is of far more importance than in trades where machines do the work under human supervision, as for instance in the textile trades. For these reasons no apology is needed for essaying to portray the miner at work, his health and occupational diseases, and efforts made for his welfare. Familiarity only with the British miner necessitates what follows having particular reference to him. Accompany him in thought

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as he leaves his home, before break of day, if he is working the first shift, on his tramp to the pit head. He is dressed in his pit clothes and carries (*a*) some cold food, put up over night and weighing with its container about 1 pound, the sort of provender which daily repetition renders unappetising and uninteresting, and also (*b*) a quart or more of cold tea, which with the can will weigh about 3 pounds. After a trudge of on an average some three quarters of a mile he arrives at the pit head where he surrenders any smoking appliances and matches, and obtains his safety lamp which weighs not less than 2 pounds. So loaded up he descends underground and, after a pause at the bottom of the shaft to get used to the dim illumination, he proceeds to the coal face, a walk of some three quarters of a mile through low passages where he must constantly stoop to avoid the uneven roof, while the going underfoot, rough and often wet, is impeded by haulage rails and wire ropes, getting rougher as he approaches the coal face. By the time he has reached his working place, our miner has expended an appreciable amount of useful energy, much of which, under better organization, might be saved for work.

FOOD

Food means for the human body, what petrol and lubricating oil mean for an automobile; it supplies the energy which is expended at work. The more work is done, the more food is needed. Hence comes appetite, the desire for food, which follows upon healthy exercise. Different estimates have been made of the daily food a miner requires; one has placed the needed energy as high as 4,700 calories, another places the average at less than 3,500 calories. Whichever be correct, the total amount should not be consumed at one sitting; it should be taken at three meals. A spell of seven hours physical effort cannot day after day be advantageously worked without food; there should be a break, when about one-third of the daily food intake is consumed, say in this case the equivalent of about 1,200 calories. The kinds of food taken naturally vary, but the British miner tends to favor bread and cheese, or bread and bacon; of these articles rather less than a pound in weight is needed of which two-thirds will be bread. In other industries the importance to output of food is today receiving attention; the factory messroom is recognized as a necessary part of

the premises; so much so that the opinion has often been expressed by the management that a well run messroom would be a paying proposition, even if no charge were made for food. But the miner, whose daily output of energy is far greater than that of the average factory operative, still works on carried food. Yet a pithead kitchen would be simpler and cheaper to organize than a factory canteen, where perhaps 700 workers or more have to be seated at once and served in five or six minutes. Meals from a pithead kitchen could be sent underground in hot, waterjacketed containers placed in empty coal tubs going to various parts of the workings. These tubs would soon reach their destinations, just as tubs containing supplies of beer did in times past, when beer was permitted to be sent into the workings. Miners do not all stop work for food at any definite time, and the service could be extended over an hour or more, thereby avoiding the rush of a factory canteen.

DRINK

Miners require to drink large amounts of fluid daily to make up for what is lost as sweat, the amount varying directly with the temperature of the workings; in one instance, at an average temperature of 99°F., the loss of moisture was found to be about 13 pounds in a work period of five and one-half hours, but from 4 to 6 pounds represents the loss in ordinary cool workings, i.e. from 2 to 3 quarts of fluid.

A capacity to sweat freely is acquired by training, and has to be regained by miners after a period away from work. Athletes know how soon staleness results if hard physical exercise is taken without an adequate allowance of fluid. A miner's working efficiency must be considerably lessened when his consumption of fluid is restricted to the amount he can carry with him. In Great Britain, at most collieries, all fluid drunk underground is brought from the miner's home and is carried below by the man. Drinking water is not supplied underground for miners, although it must be supplied at the stables for pit-ponies. Here again the miner is worse off than factory workers, since wholesome drinking water must be supplied in every factory.

In America the position in this respect is somewhat better, but still, I understand, is far from ideal.

SALT

Closely associated with the question of fluid lost as sweat, is the fact that sweat contains salt, and that anyone who sweats copiously loses at the same time a lot of salt; finally a shortage of salt in the blood and the muscles results. If plain water is taken to assuage thirst, what is known as water poisoning results with distressing symptoms of muscular cramp. Cramp of this kind occurs among miners in hot mines, among furnace men, and among ship stokers; in severe attacks several men may be required to control the sufferer and straighten out the affected limbs. If, however, the water drunk contains about 10 grams of sodium chloride to the gallon, cramp is avoided, less fluid is needed to satisfy thirst, and fatigue from exertion more rapidly passes.

Two facts may here be noted. Where barley is drunk by men at hot processes, the custom has always been to flavor it with salt. The amount of salt consumed daily in food was found to be considerably greater for miners employed in hot mines than for men working in cool mines.

ALCOHOLISM

A word may not be out of place here concerning the alcoholic habits of coal miners who have in the past maintained a reputation for "convivial" drinking. They are not "industrial" drinkers. No alcohol can be obtained after going below; when the effect of a dose taken before commencing work passes off, another dose cannot be obtained. The resulting effect is so unpleasant that the miner holds he cannot do his work on alcohol, and, for the most part, takes none until the day's work is over.

Herein, he differs from such men as dock laborers, who throughout the day have recourse to refreshers. Mortality records indicate that industrial drinking, i.e., drinking before and during work, is far more harmful than convivial drinking; thus, all coal miners in England and Wales, during the years 1910 to 1912, experienced a comparative mortality figure due to alcoholic diseases of only 9, while that for dock laborers was 30, and that for all males, 17. The suggestion may be made that the provision of suitable drinking water underground would diminish fatigue, increase productivity, abolish cramp and reduce

alcoholism. The reason why the miner is a convivial drinker is not far to seek; he leaves the pit soiled with the color-bar of his occupation; tired after work, a tiredness accentuated by his poor food supply; thirsty from losing more fluid by perspiration than he has had drink to replace; his clothes cold and damp with sweat. His tired body calls for a sedative, for fluid and for warmth. Alcohol is a sedative; it is consumed diluted with water; it is to be procured in a warm bar parlor. Hence, an alcoholic beverage is the ideal to meet his present need, even though far from being a future blessing.

VENTILATION

The amount of sweating a miner does depends largely upon the temperature underground and also upon the humidity of the air and its rapidity of movement. The greater the cooling power of the air, the less he sweats and the better he can work. To enable the skin to sweat, blood, which would be better employed in the muscles, has to be sent into the skin. When the muscles are working and the skin is sweating, the heart has to do double work to keep both supplied with blood. One object of ventilation from the health viewpoint is to ease the work of the heart by keeping cool refreshing breezes playing over the skin. But in coal-mines quite different objectives determine ventilation; first, in naked light pits which are seldom hot there must be enough oxygen for candles to burn; secondly, in safety lamp pits ventilation is employed to dilute explosive gases coming from the coal and to sweep them out of the workings. The miner has benefited greatly by modern mine-ventilation; but as pits are sunk deeper and so become hotter, the need for cooling increases, while the need for diluting explosive gases may not. A miner at work is in no way affected by breathing a highly explosive mixture of methane, or black damp, and air, but is seriously affected by a chemically pure, but stagnant and humid atmosphere of over 84°F. Research has already demonstrated that the activity, which spells the productivity, of miners decreases as the cooling power of the air in the workings decreases, and that when the cooling power is increased the output of coal is increased. The cooling power of air can be increased by increasing its movement without altering it in any other way. Here is a form of ventilation, frequently obtained in restaurants and theatres by gyrating paddle

fans, which has not yet been explored for mines. One investigation revealed how in a stagnant warm atmosphere, at 79°F., miners naturally rested some twenty-two minutes every hour and took nine and one-half minutes to fill a tub with coal, while when the cooling power was good, at 66°F., they only rested about seven minutes, and filled a tub in eight minutes; their working capacity was increased from 35 to 41 per cent.

LIGHTING

The distinctive characteristic of coal mining is darkness; black walls, black floor, black roof, reflecting a minimum of the light which glimmers from the safety lamps, a light five times less than the illumination from a single candle. Constant exposure day in, day out, performing manual labor, for which vision is needed, in such a gloom is associated with a curious, distressing disease of the eyes—miners' nystagmus. The eyeballs oscillate rapidly which means for the sufferer that the outside world seems constantly to be on the move; but the oscillation often exists without the miner appreciating it and without causing any disability. Later sight is affected, headache and giddiness on stooping develop, broken sleep, dread of light, and neurotic symptoms. Absence from work always cures the oscillation, but by no means always the neurosis which may persist and lead to chronic invalidism. Prevention lies in better illumination underground and cure in resumption of work in daylight before returning below. Compensation is awarded for disability caused by nystagmus, and more claims occur in Great Britain for this disease than for all other compensable diseases taken together.

Nystagmus represents an accentuated end-result of dim illumination, but by no means all the results. Many accidents (to which reference follows) are caused by lack of light; while one inquiry established that output can be increased 10 per cent by better illumination.

The statement in the report for 1925 of the Secretary for Mines is surely true: "More light is, perhaps, the greatest single contribution that could be made to greater safety and improved health and efficiency in underground work."

MINERS' BEAT KNEE, BEAT HAND AND BEAT ELBOW

Miners have rather a monopoly of compensatible diseases, as, in addition to nystagmus, they claim beat knee, which stands second on the list, beat hand which comes third, beat elbow and synovitis of the wrist, each of which is about equal fourth with dermatitis, followed by lead poisoning. Thus in 1924 the claims were:

Nystagmus (new and continued cases)	10,906
Beat knee, Beat hand, Beat elbow, Synovitis of wrist	4,680

TABLE 1

Compensated cases of disease in Great Britain, 1919 to 1924

DISEASE	1919		1920		1921		1922		1923		1924	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Nystagmus:												
New	2,718		2,865		1,913		4,092		3,883		3,271	
Old	3,731	91.1	4,163	90.3	4,804	94.0	5,063	94.9	7,273	93.9	7,635	92.5
Beat knee, hand, etc.	2,726		2,380		2,021		3,492		4,679		4,680	
Dermatitis	270	2.7	408	3.9	279	3.0	319	2.4	534	3.2	709	4.2
Lead poisoning	231	2.3	265	2.5	230	2.5	273	2.1	381	2.3	449	2.7
Other diseases	398	3.9	344	3.3	43	0.5	83	0.6	115	0.6	108	0.6

a total of 15,586 out of 16,852, or 92.5 per cent, leaving all other compensatible diseases, including anthrax and poisoning by lead, mercury and arsenic, dermatitis and epithelioma to account for only 734 claims.

The three "beats" are postural troubles, local chronic inflammations due to frequently repeated injuries. As the miner lies on his side, undercutting coal, the outside of his knee comes in contact with the hard floor and a swelling develops locally under the skin. If this swelling becomes infected, suppuration follows and the case is one of beat knee. Beat elbow has a similar origin, but acute swelling without infection is more frequent, and spicules of bone are liable to separate from the point of the elbow. Beat hand is due to using picks with

rough handles and to jars from working hard coal and rock; the palm of the hand gets infected, or infection spreads there from an infected finger. Suppuration follows, and, unless the case receives skilled surgical treatment, a contracted, useless hand may result. Knee pads and smooth pick handles are simple preventive measures far too little considered. (See table 1.)

RHYTHM AND METHOD IN WORK

These postural diseases introduce the question of how miners work. Coal mining is no exception to the custom in industry to leave each manual worker to discover for himself the best way of using his own body. No organized scheme is adopted, as in the field of sport, to teach how a blow should be struck or strength used; the boxing instructor and the golf professional have no counterparts in industry. Instruction in how to play is taken seriously, but is disregarded in the matter of how to earn a livelihood. A short study of rhythm in coal getting has been made. The best miners were found to use a comparatively slow stroke of the pick in getting coal and a faster one working on harder rock; the rate of stroke also increased with the hardness of the coal. The quicker rate for hard material arose from utilizing the rebound of the pick; in the softer coal, the point of the pick tended to stick and a slower stroke was needed to allow time for withdrawal without losing the rhythm. A metronome was introduced and set beating to the rhythm of the best miners; other groups of miners, one after another, were induced to follow the rhythm set by the metronome. Once taught, the men were found able to maintain the rhythm on their own initiative. Calmness now characterized work which previously had appeared spasmodic, while output increased from 6 to 16 per cent. These results were obtained with old miners, but, if similar training were given to young men just beginning to work who had not already formed contrary motor habits, still better results should be obtained.

DUST IN COAL MINES

Whatever methods of work a miner pursues, his occupation is a dusty one. Dust is generated when coal and rocks are broken. Fortunately pure coal dust is not injurious to breathe. But coal is seldom

pure; it contains foreign materials such as grains of sand and the like. If the proportion of these materials is high, the dust worries the air passages, and a tendency to develop bronchitis and pneumonia results. Where much sandstone rock has to be drilled, a further dust risk is introduced, since fine sandstone (or silica) dust has the special property of predisposing to phthisis; this risk, however, only concerns the small group of miners that drives roads and sinks shafts in sandstone, and the occurrence among them of true miners' phthisis, such as occurs among gold miners and tin miners, had, until quite recently (although suspected) escaped detection.

An entirely different risk is associated with dust in coal mines. A mixture of fine organic dust and air is explosive. In mines, coal provides the organic dust. Chance ignition of inflammable gases emanating from coal may start a wave of detonation. Such a wave disturbs coal dust lying on the sides and floors of the galleries, wafts it into the air and so forms a mixture which, in its turn, explodes and passes on the wave. In this way, ignition of a small pocket of inflammable gas in one corner of the workings may initiate an explosion which travels far and near throughout all the roadways of the mine.

If, however, the coal dust on the floor and sides contains about equal parts of fine, inert dust, then the mixture formed with air has been found not to be explosive and to be incapable of passing on a detonation wave. Discovery of this fact has led to the adoption of the practice of dusting the roads of coal mines with inert stone dust. The question has then arisen whether the dust so introduced may not introduce a further danger of its own from dust inhalation. Mortality data from other industries indicate that no danger is to be anticipated from the use of limestone dust which, moreover, being light in color, has distinct advantages from the point of view of nystagmus. Dusts containing silica are to be carefully avoided and no material should be used about which any suspicion can arise.

Probably no dust, if inhaled in sufficient amount, is entirely harmless. Hence the process of stone dusting needs to be carefully regulated. It should be done when there are as few men as possible in the workings, and those employed should proceed down the air current so that the dust does not blow back, but is rather carried away ahead of them.

The value of stone dusting for preventing explosions cannot be

doubted; the probability of any ill resulting from dust inhalation is small under good practice, but the certainty of its harmlessness can only become manifest after years of experience.

EXPLOSIONS

Great mining disasters due to explosions are today far less frequent than twenty years ago. When an explosion occurs underground, there is never enough oxygen present to allow of complete combustion of all the carbon, i.e., the coal dust present; hence, instead of carbon dioxide, large amounts of the more deadly carbon monoxide are formed. It is this gas which causes most deaths when explosions occur in coal mines, and it is against this gas that the rescuer, going into the workings after an explosion, must be safeguarded. Such a rescuer is fitted with an apparatus which supplies him with fresh oxygen without having to breath the air in which he is moving; in fact he carries his own atmosphere with him. When any gassed miner is found, he has to be got into an atmosphere free from carbon monoxide and then brought round by artificial respiration, for which purpose oxygen, reinforced with carbon dioxide, is of great value. The carbon dioxide stimulates the patient to breath, while the oxygen gradually turns the carbon monoxide out of the blood and takes its normal place.

Research carried out with rescue apparatus has led J. S. Haldane to claim that a miner (and probably any other athlete) when in training, acquires the power of secreting oxygen through the alveolar cells into the blood stream, instead of leaving the gaseous interchange between the alveolar air and the hemoglobin to be a matter entirely of the physical process of diffusion. This means that less air is breathed by men in good training for a given consumption of oxygen or amount of work. Such lung fitness is an accompaniment of general physical fitness.

The facts regarding the fitness of a trained man are definite; but the explanation may lie rather in the power of his muscles to abstract oxygen quickly from the blood, than in any power of the lungs to secrete it inwardly from the alveolar air.

PITHEAD BATHS

The miner at the end of his shift is black with coal dust, which gets beneath his clothes and soils his whole body; he is tired and his underclothes are cold and wet with perspiration. If the mine is a warm one, as is not unusual, when the miner is drawn to the surface he is on most days exposed to the chilling effect of a sudden alteration of temperature. No other group of workers have greater need for an opportunity for bathing and changing into dry clothes before travelling home. The case for pithead baths is unanswerable. They are required in the interests of efficiency and health; of absenteeism which is higher in wet weather for lack of change rooms; of the self-respect of the miner, who is avoided in train and tram by people in clean clothing—a matter of no small import to his psychology; and, not least, of the miner's wife. Her work, over and beyond her usual domestic duties, is continuous. Meals to prepare and food to put up for men working on two shifts, hot water to have ready when they come home, and dirty wet pit clothes to dry. As few miners' homes have baths, the wash is taken in a wooden tub or iron pan before the kitchen fire, while wife or daughter assists the stark man by rubbing down his back. After some delay this matter is now to be rectified; the duty has been placed by Parliament on the Miners' Welfare Committee to provide, out of funds allocated for the purpose, pithead baths throughout the industry.

The need for action in this matter may be gathered from the facts that in 1923 bathing accommodation only existed at the pits of Great Britain for less than 7,000 men, and that it had only been increased by 1925 for less than 20,000, while 1,000,000 miners go below ground daily.

ACCIDENTS

Of intent, consideration has been postponed till now of the most serious risk to which coal miners are exposed, the accident risk. Their mortality from accidents is only exceeded among industrial groups by seamen; it amounts to nearly one-sixth of all deaths, as compared with one-seventeenth for all males. It accounts for an annual death rate of about one per 1000 British coal miners, a rate which compares favourably with that for miners in other countries, but unfavourably

with a rate of one per 7000 factory workers. Or again, one British coal miner out of every 5 sustains a disabling accident annually as compared with one out of every 26 factory workers. Compensation statistics for 1924 bring out the importance of accidents to the industry:

	MEN EMPLOYED	NUMBER OF ACCIDENTS	COST PER PERSON
			s d
Shipping, factories, docks, quarries, building and railways	6,309,762	259,378	10 5½
Mines	1,202,597	230,942	56 2

The total cost of compensation during the year was £6,675,038 of which £3,376,214, or 50 per cent was claimed by the 19 per cent of the workers belonging to the mining industry. In these totals, cases of occupational disease are grouped together under the heading "accidents." The risk must always be great from falls of roof, explosions, haulage and other causes associated with working in dimly lighted, rough, underground passages. Nevertheless mortality from accidents varies on different coalfields, and varies in an interesting way; it varies as mortality from other causes, particularly from respiratory diseases, varies. The orders obtained by arranging the coalfields according to mortality from accidents, or from bronchitis, or pneumonia, or phthisis, nearly coincide. The deduction obtrudes itself that conditions which lead to ill health, particularly of the kind which terminate in death from respiratory disease, have also some underlying influence on accident causation; probably the ill-being which the conditions cause is at the root of the matter. "Carelessness" with regard to safety is largely an expression of ill-being; a man who is healthily alert is not naturally careless. Indeed the question may fairly be asked, not only for coal mines, but for the world at large, "Are accidents accidental?" The personal factor cannot be entirely eliminated even from explosions and shaft accidents. In factory employment this element has been calculated to account for not less than 80 per cent of all accidents. It is probably at least as important in mining.

Many of the things here advocated—improved illumination, food kitchens, drinking water and pithead baths—would, by improving the health, efficiency, and self-respect of the miner, have an indirect, but

considerable, influence in reducing the frequency of these "personal factor" accidents. They require, however, to be reënforced by that form of education known as the safety-first movement; already a few colliery managers have initiated this movement with marked success. Nevertheless, up to the present the personal factor in the causation of accidents in mines has received far too little attention.

MORTALITY AND PSYCHOLOGY

The mortality records just instanced have further interest. The statement is often made that contentment in life is dependent on health, and dissatisfaction on ill-being; it is a difficult statement to justify by figures. Ballots were taken of the miners of Great Britain on three recent occasions; they may be regarded as direct indications of the extent to which dissatisfaction prevailed on the different coalfields. The orders of the fields are not only curiously alike on the three occasions, but are closely similar to the orders obtained by mortality records, so close as to be outside the likelihood of chance occurrence. One interesting apparent exception in the order of 1920, according to ballot, should be noted: Yorkshire is clearly out of the position which mortality records ascribe to it. But on this field a strike occurred in 1919 which did not involve other coalfields, and the effect of this event was held to modify the votes cast for the strike in 1920. In 1921 and 1924 when all the coal fields started from the same basis, the percentage vote indicative of dissatisfaction places Yorkshire much more nearly in the order according to mortality records for 1910 to 1922. The way to remedy this psychology, with its results so paralyzing to the community, is to alter the conditions which give rise to it, so that ill-being and ill health are reduced to a minimum. Much can be done during working hours by providing pithead kitchens, supplying drinking water, improving ventilation, increasing illumination, teaching methods of work, controlling any dust risk, installing pithead baths, and pursuing safety first methods.

WELFARE SCHEMES

But working hours do not cover the whole day, and the home life on coal fields leaves much to be desired. Mining villages are drab places,

generally rather isolated, owing to the position of the pits, from other industrial centres.

An organized effort was started in 1920 to improve these conditions. A statutory levy is made of one penny on each ton of coal raised. The fund so gathered, which is known as the Miners' Welfare Fund, amounts to approximately one million pounds sterling per annum; it must be applied to purposes connected with the social well-being, recreation and conditions of living of workers in or about coal mines and with mining education and research. A sum approaching four million pounds has already been expended, of which about two millions have been devoted to institutions and recreation schemes; here the very appearance of the country side has in several cases been altered, alterations which have affected not only the country, but also the miners.

About one million pounds has been expended on health projects, such as assistance to hospitals and the establishment of convalescent homes, either by constructing new ones, or converting existing mansions. Half a million has also been devoted to research, and half a million to education. The duty of allocating moneys from the fund is entrusted to a small committee to whom in 1926 the further duty was given of supervising the construction of pithead baths, together with further moneys for the purpose (levied on royalties).

My object in this lecture has been by taking the occupation of coal mining as an example, to display the importance of the human factor in industry, and vice versa the great influence for good which industries, acting through those employed, can and should exert upon the health of the community. Any other industry or trade might have been chosen to point the moral that occupations exist first to give health, whence springs wealth, rather than to manufacture wealth while leaving health to look after itself.

THE ENVIRONMENT IN RELATION TO HEALTH[1]

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INTRODUCTORY

Man has been said to be a product of heredity and environment. Heredity represents an endowment from the past, an ancestral estate to which each individual falls heir at birth and which he must accept whether it be good or poor, to do with what he will. Environment represents the present day opportunity to develop that inheritance, to make good use of a poor inheritance or a poor use of a good one.

However seriously biologists may debate the relative importance of these two factors in the development of mental and moral traits and character, it is quite plain that in regard to physical health and well-being there is no hereditary endowment so good that it cannot be wasted away in a bad environment, and rarely one so bad that it cannot be reclaimed, in part at least, by favorable treatment. This is so because life itself is a flowing thing similar in many respects to a stream of water. Regardless of its source and early history such a stream adapts itself to the varying physical contours of its banks and moves sluggishly or feverishly according to the slope of its bed. It may become fouled by passing over filth and be restored to cleanliness and purity under the influence of air and sunlight. So it is with physical life; confined within fixed boundaries, and urged by the very laws of its being to move along established channels, it is nevertheless molded and directed, stimulated or retarded, contaminated or purified by its contacts.

In less imaginative, but more concise and descriptive phases the great biologist, Herbert Spencer, spoke of life as being characterized by a continuous adjustment of internal to external relations, or, in modern terms, by adaptation of function to environment. The degree of this adaptability is great. We see it illustrated for example when

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men, presumably made of the same protoplasm, are found existing in apparent comfort and well-being under the direct rays of the tropical sun and far within the arctic circle; under conditions of extreme poverty and deprivation and under those of luxurious wealth; in the dampness and darkness of a mine, far beneath the earth's surface, and at such mountainous altitudes that the actual atmospheric pressure is reduced by one-fifth of its normal value. In fact, viewing life as a whole, there seems to be almost no limit to its adaptability if the rate of change of conditions be sufficiently slow. The sperm whale in the depths of the arctic sea and the bird of paradise in the tropical forest are merely suggestive of these possibilities.

Our present interest, however, centers not so much upon the limits of adaptability as upon that other important characteristic which we speak of as the most favorable or optimum condition. We cannot believe that human existence is functioning best under any of the extreme conditions to which allusion has been made. In whatever direction we may extend our search we always find, between the extreme limits of adaptability, within which life may actually exist, a certain, much more restricted range where the life processes function most smoothly, and with least danger of overstress and breakdown. This is the range of conditions within which the forces of evolution appear to operate most effectively, because least disastrously, and where progressive improvement, rather than mere static existence, seems to be really worth while. It is one of the problems of public health to investigate and to define as far as practicable this optimum range of conditions.

To show that this is a very practical problem requires, I think, but little discussion. In the rapidly changing conditions of present-day existence, we have learned, not only to define and to avoid the definitely harmful, but also to seek out and to utilize, as far as possible, the more beneficial, conditions. But we go further than this. We are to-day very largely in control of our environment. Just as it is possible to provide, in this room, by suitable engineering devices, an atmosphere of any specified physical properties, so in general, we may modify the external conditions, that are unfavourable and manufacture, if need be, others that are desirable. Thus by clothing and housing we protect ourselves against unfavourable climate; by lighting, we

lengthen the working day; by transportation we bridge distance and bring the world's food to our kitchens.

This situation is of course limited by the temporary limitations of engineering skill. But it is limited also by our own lack of knowledge. Just as in the illustration given, we must know what air conditions are desirable, before setting up the equipment to provide them, so in general we must know the optimum conditions of living, before putting into effect the machinery of control.

The public health engineer of today, is, in brief, and to a large and increasing extent, developing the complement of Spencer's definition of life and continuously adjusting external to internal conditions. Our present inquiry then, takes this form: What are the important contacts with the environment, as they affect the health of man? What are the undesirable and what, the most favourable conditions of the environment at these points of contact?

Just as the actual physical environment is made up of a multitude of separate units, none of which is capable of individual existence, so the problem of the optimum environment is not one capable of a single solution. For example, the respective climatic conditions of New York City and of Los Angeles, conditions over which we have no primary control, throw into greater or less prominence many of these artificial factors with which we actually have to deal. The problem of ventilation of schools, which presses most seriously in northern cities, could hardly be considered a practical public health matter in a more equable southern climate. In the preservation of food it is quite obvious that our problems, especially during cold weather, are much simpler than theirs. Nor is it necessary to compare places of different climates to develop this point. In the matter of clothing, for example, an environmental factor of some importance, the most favourable arrangement may, within a brief period of twenty-four hours, and within this city, be represented variously by a rain coat, a top coat or a palm beach suit.

The most favourable condition of temperature, furthermore, is dependent upon the occupation of the individual, whether he be engaged in hard manual labor or occupying the easy chair, shall we say, of a public health official. If we will examine our problem still more minutely we may find that even between individuals, at the same time

and place, and under apparently the same physical conditions there is variation of requirements. In our northern cities the disagreement between husband and wife as to the proper household temperature is a proverbial matter, and even among those of the same sex there are innumerable individualities, possibly remnants of heredity, which make for characteristic personal preference as to food, clothing and other physical contacts with the environment. Our study then must take full cognizance of this manifold individual difference in addition to the mutual inter-relation of the various items which go to make up the environment in toto. We can hope at best to locate upon this confused chart, average conditions and limited ranges, sufficiently broad to include normal individual variation, and sufficiently restricted to establish regions that are best suited for normal life and development.

THE ATMOSPHERE

Let us now give some thought to a few of the sub-divisions of the total environment with which our public health measures have most to do. Most intimate and most universal of these is the atmosphere. Air is the least dispensable of all the environmental factors. A man may live for days without water and for weeks without food. His ability to go without air, however, is limited to minutes. This is not a mere accident. It results from the fact that air is ever present and under no normal situation does a human being find it necessary to go without or even economize in its use. Capacity for storage of air within the body would be without value except possibly in a race of pearl divers. Food supply, on the other hand, has only become continuously available through the operation of a highly specialized social organization, and even then in strictly limited quantities. Among primitive peoples it depends to a large extent upon climatic vagaries and the fortunes of the hunt. Hence the necessity for some mechanism whereby available food may be stored during times of plenty against times of scarcity. Water occupies a somewhat intermediate position. As a rule it is readily available in habitable regions, but neither continuously so nor in such excessive quantities as is air. We find then a capacity for temporary storage of water within the body intermediate between those for air and food.

The open air presses closely against all the external surfaces of the

human body, and, by means of the respiration, freely bathes a large internal surface. The circulation of the blood carries its component parts to every organ and tissue. This intimate relation between the human body and what the late Professor Sedgwick has called its aerial blanket makes a study of the atmosphere and its control one of the first considerations of our survey of the environment.

In its broadest aspect this study is a study of climates, and for this purpose the whole world becomes our laboratory. By applying the principles and data of climatology we endeavor to ascertain what is most beneficial and what most harmful in matters of external temperature, humidity, wind movement, sunshine, fog, ionization, electrical potential and other climatic features, and in the diurnal and seasonal variations in all of those. Professor Ellsworth Huntington in his "Civilization and Climate" has shown a rather marked tendency toward a grouping of the more advanced nationalities of the human race in those regions which are moderate in all their climatic factors, both as to average values and as to the ranges between extreme values. It is unnecessary, in order to appreciate this fact, to decide whether moderate climates have produced civilization or whether more civilized man has sought moderate climatic conditions.

It must be obvious, from what we know of adaptation, that a given race, or a given species, will develop adaptability to a range of conditions which extends about equally above and below the most favorable condition. Or, putting the theorem in a more nearly self-evident form, adaptability to a given range of conditions automatically establishes an optimum condition at about the middle point of that range. Thus with the human race, adapted to live under the Equator and within the Arctic Zone, one would expect an optimum condition of living under temperature, and other physical conditions approximately midway between these two. This theorem, if valid, may possess some value to us in our search for optimum conditions, for it often happens that the limiting conditions are rather sharply defined. We will attempt only a single rough test as follows:

According to Professor Robert Ward, in the Encyclopaedia Britannica, the mean annual temperature over a considerable portion of the tropical land areas of the world lies between 79 and 90 degrees, or say, approximately 85 degrees. Within the inhabited portions of the

arctic regions mean annual temperatures range between 32 and 10, or for the average about 21 degrees. This gives us a midway temperature between the tropics and the arctic of about 53 degrees. Professor Huntington finds that a mean annual temperature of about 51 degrees is the optimum for health, and for both mental and physical activity. The same general relation seems to hold with respect to daily and seasonal variation, especially the latter. In various portions of the zone of satisfactory mean temperature there are regions with little or no variation, and regions of great variations. Huntington finds that the optimum conditions are those of moderate variation, ranging about the mean by not over 7 degrees either way. Similarly, in any one locality, we know there is a maximum degree of comfort and enjoyment during those seasons which represent most nearly the annual temperature and during those periods likewise when there is neither extreme rainfall nor extreme drought.

In brief we find the human organism thriving best under moderate or temperate conditions, whatever be the direction of our investigation.

Coming now to the more immediate atmospheric environment, the subject of air pollution is one that engages the attention of the sanitarian. In the broadest aspect this leads us to a consideration of atmospheric pollution by the smoke and dust of cities. It has long been an accepted biological thesis that green plants are directly dependent upon solar radiation for their vital activity, and that man and the animals are similarly dependent only indirectly through their food requirements. It may be that this conception was fundamentally wrong, or it may be that changes in our mode of living, especially our increasing use of canned and preserved foods, has upset a delicately balanced system. Whatever may be the true fact it is now amply demonstrated that man can utilize solar radiation directly, to produce in the body essential vitamines, and that the growing child needs this radiation, or its equivalent in a carefully considered diet. The established relation between the prevalence of rickets and absence of sunshine serves well to illustrate the important fact that limited adaptability to unnatural changes in certain essential environmental factors may be one of our most important inherited characteristics.

Certain it is that the ever increasing pollution of the atmosphere by the smoke, dust, fumes and odors of industrial processes constitutes a

departure from the normal so great as to warrant the most thoughtful attention of sanitarians. Whether we should in all cases await definite statistical evidence of harmful results, or whether we ought to place the burden of proof of harmlessness upon the offender may be a debatable matter. Heretofore, we have adopted the first named course, especially in the industrial world and have made full scale experiments upon human beings, often with disastrous results. Our experience in the past with phosphorus and with lead, in industry, to mention only two well proven cases, are typical of this procedure. Future studies may show that the gross pollution of the air over our industrial cities is likewise too great a departure from the normal to be tolerated by human beings, and the wisdom of the future may lay down the rule that no serious modification of any essential environmental factor may be made without satisfactory evidence in advance of its harmlessness.

A still more restricted view of atmospheric pollution draws our attention to the problem of ventilation. To enter into a full discussion of this important problem of public health engineering would carry us far beyond any reasonable limitations of a single address and is unnecessary for our present purpose.

The air is continuously contaminated by the gaseous products of respiration, and were it not for the ready diffusibility of these products air pollution would rank with water pollution, a problem of first importance in sanitary science. Fortunately, the exhaled breath is rapidly diffused in the surrounding atmosphere, so that it is only when we confine numbers of human beings in enclosed places that ventilation becomes a problem in hygiene. Furthermore, we have now learned that even in such cases it is not the chemical pollution of the air but its physical modification which gives us most concern. Air performs many physiological functions, among which is the function of cooling the body. It happens that under conditions of restricted air supply this function is the one which first reaches the point of failure. The problem of ventilation of enclosed, occupied spaces, therefore, is primarily one of cooling.

This fact is of interest, because it presents for our study a new type of optimum condition. The cooling properties of air are determined by its temperature, its humidity, and its rate of movement past the body. These three characteristics are independently vari-

able, so that there are many sets of air conditions having the same physical cooling power. Thus, starting with any given condition, the temperature may be raised and the humidity lowered by appropriate amounts to maintain a constant cooling power. Or again, either of these changes may be made and its influence offset by a change in air velocity.

In some recent work, sets of equivalent cooling conditions have been determined by the subjective test of feeling and those combinations giving the same sensation of coolness have been defined as of the same "effective temperature."

Aside from the questionable propriety of testing cooling conditions by the momentary skin reaction to a changed condition, this conception of effective temperature ignores the basic physiological facts upon which our whole problem rests. Let us grant that a series of conditions exist, ranging from hot and dry to cool and moist, to consider only two of the variables, any set of which will remove the required number of calories from the body during a unit of time. Suppose the two end points of such a series are 65 degrees and 100 per cent relative humidity, and 75 degrees and 50 per cent relative humidity, respectively. In the one case cooling is largely by the normal process of conduction, in the other by excessive evaporation of the perspiration. Now cooling by evaporation is the body's last resort short of fever. It is a normal accompaniment of hard labor in warm air and is followed by fatigue. When induced in a person of sedentary habits by excessive room temperature it is abnormal and is in no sense the physiological equivalent of cooling by conduction. The fact that the required amount of cooling is accomplished is entirely beside the point. An arctic explorer, in his furs, and a swimmer in the surf of Atlantic City may both be disposing of the same number of calories per hour, but one would hardly class the two environments as equivalent.

We find in fact that for any particular age and occupation, such as children at school, and with appropriate clothing, there is an optimum condition of the air, fixed within rather narrow limits as to temperature and velocity. In this specified group under proper temperature conditions, perspiration is of the insensible sort, and evaporation is complete within wide ranges of humidity. Hence variations of humidity do not affect the rate of cooling. In a group of mechanics, on the

other hand, the optimum condition is further restricted to a humidity sufficiently low to permit cooling by evaporation of the sensible perspiration accompanying their greater activity.

In brief, ventilation of enclosed and occupied places should provide air conditions suited to the customary clothing and activity of the occupants. It is one thing for a gymnasium and quite another for a class room. For every situation there is, in general, a physiological optimum, which must be determined either by physiological experiment, or perhaps better, by statistical measurement of the health, fatigue, productivity or other results of varied atmospheric environment. Equivalent physical conditions, and their correlaries, effective temperature and zones of comfort are of little help to us in this connection, and their use may lead to gross misconception of the facts upon which the modern scientific views of ventilation practice are based.

WATER

When water is considered as an environmental factor, one notes at the outset that only for the fish and other aquatic forms of life, does water constitute the kind of intimate environment that we have thus far discussed. For man, water and food are more property environmental contacts. As such they have tremendous public health significance. Between the hands of the fig packer in Smyrna and the mouth of the consumer in Baltimore, the protective agency of distance has been eliminated and the two are brought into virtual contact, save for that other protective agency, the lapse of time. This aspect of the environment is not wholly lacking in the case of air, especially in connection with insect borne disease, but it is the fact of outstanding interest in any consideration of water supplies.

Natural waters are the necessary final depositories for many of the varied wastes of nature. Generally these wastes, consisting of organic débris washed from the soil, are in themselves quite harmless. It is only when the waters become fouled by human excreta that they become dangerous to human beings. It has remained for modern science to show how easily water courses may thus become polluted, and how they may carry the germs of infectious diseases over long distances and for considerable periods of time.

As a problem in public health engineering, therefore, the provision of a safe water supply may involve consideration of preventive measures at points of pollution, of self purification of the stream by natural agencies operating between the point of pollution and the point of use, and of purification measures, applied at the latter point.

While sanitarians are quite in agreement as to the desirability of maintaining streams and lakes in a condition of purity, this has not always proved feasible. In the more congested parts of the world it has been found necessary to utilize these same bodies of water to carry off the drainage and sewage of cities. Even though this be safeguarded by modern and efficient methods of treatment there still remains an irreducible minimum of dangerous pollution to which must be added pollution from rural districts, navigation and other sources, so that we are forced to assume that all natural waters in populous areas are dangerously polluted. Thus, despite our efforts at prevention, some remedial measures are clearly indicated. The purification of water supplies, therefore, has become an important item in the sanitary programs of cities. By this means immediate and often spectacular lowering of death rates has occurred. I would remind you, however, that it is not water purification, the curative measure, that interests us primarily in our study of the most favorable environment. If we have anything to learn from the mistakes of the past, it is that early prevention of conditions of stream pollution by such means as are available at the time, will, in the long run, advance us more in the scale of sanitary excellence than anything that can be done later to remedy the effects of early neglect. In the United States we have some reason to boast of the great saving in lives that has been brought about through the introduction of water purification. But it should be a matter of considerable shame that for so many years these lives were needlessly sacrificed.

We cannot at this time go into the many interesting details of the various processes of water and sewage treatment. The history of their development provides a story of scientific achievement of dramatic interest. Of equal practical, as well as scientific value, are the studies of the self-purification of streams with which Dr. W. H. Frost has been so closely and so creditably identified. We have learned how to measure the capacity of a stream to receive and dis-

pose of pollution. The knowledge makes it possible for us to plan our works so as both to conserve and to utilize our available stream resources, to the end that a maximum beneficial use may be made of them.

RURAL SANITATION

In country districts the protection of the water supply of the household from pollution by its own wastes constitutes nine-tenths of the problem of rural sanitation. Yet these seemingly simple situations have never yet been worked out to a point of a general and practical solution, if we set up as our criterion the general adoption and satisfactory maintenance of any of the systems proposed. There are, it is true, many paper solutions, and no doubt we have the necessary knowledge, but there seems to be more of a human element to this problem than to most others, or at least a human element of a more difficult kind. Our final solution must of course include this element as well as the others.

FOOD

Food, like air and water, may be considered as an environmental factor essential to the life processes, and in the study of this phase of the subject, the modern science of nutrition has made notable advances. It is not our present purpose, however, to inquire into matters of protein, fat and carbohydrate, of calories and of vitamines, interesting and valuable as such a discussion might prove in the hands of one qualified to deal with them.

From another point of view food, under modern conditions of living, constitutes an environmental contact of much greater significance than any that we have thus far considered. In the first place the range of the effective environment is still further increased. In the markets of our large cities may be found foodstuffs from every quarter of the world. One day we read of a fruit handler in New York being bitten by a tarantula from the West Indies, another, of an English embargo on American apples, suspected of carrying too great a residue of arsenical spray. Chicago pork products are inspected to prevent trichinosis in Germany, and only last week milk and cream from Montreal was barred from Boston and New York because of possible typhoid infection.

Not only are world-wide distances thus bridged by present-day methods of rapid transportation, but the foods themselves, unlike water, often provide an ideal medium for the preservation and even the multiplication of certain specific organisms of disease. Thus initial infection of relatively harmless proportions may eventually produce a serious outbreak of disease.

A third characteristic of food supplies results from the tendency toward mass production and distribution to meet modern city requirements. The danger increases with increasing size of the production and distribution unit, for each infective center then exposes a greater population, and conversely each consumer is exposed to more infective centers. The history of milk-borne epidemics is a history of large milk supplies, not of a scattering of the disease over a large number of small supplies.

The problem thus arises with the development of community life. It can be illustrated by the milk supply of a large American city. The New York City supply involves an average daily shipment of over three million quarts of milk and over 150,000 quarts of cream, from a geographical area extending over five hundred miles to the north and west. It is estimated that not less than 45,000 farms and probably more than 100,000 employees are engaged in the production of this milk supply. If we add the large numbers of men engaged in handling and distributing it, it is apparent that the danger of an initial infection is great, and, even through this enormous volume of milk is in fact divided into many independent distribution systems, there still remains an opportunity for dissemination of disease in epidemic proportions.

Here again we have a picture of early laxity, due partly to ignorance and partly to the natural inertia of the community. Typhoid fever, scarlet fever, diphtheria, septic sore throat and other diseases of less importance appeared at frequent intervals in the form of sharp epidemics, clearly of milk origin. To complete the picture it is only necessary to recall that a large proportion of the cattle, and practically all the herds were tuberculous. Tuberculosis of the bovine type was consequently a common disease of infants. Pasteurization of milk, which has become a well-nigh universal practice in the larger cities and is commonly practiced in most places throughout the United States

has undoubtedly had a very large share in the important reductions in death rates and sickness from these causes, which has been noted in recent years.

This is probably the most striking example that can be cited of the dangers of a city food supply and of the magnitude of the administrative effort involved in their satisfactory control. Many other foods are similarly involved.

In fact the germs of infectious diseases often find an easy mode of transit from patient to victim along the food route so that the protection of foods from dangerous contamination becomes one of the important sanitary problems of modern city life.

There is another aspect of this subject which is of indirect rather than direct application. Briefly stated it is that any agency which detracts from the quality, appearance or palatability of a food discourages its use throughout the general population. This matter has been made strikingly manifest in the history of the New York milk supply. With gradually and steadily improved quality and appearance, and with the general introduction of the glass bottle container and the consequent elimination of visible dirt and improvement in cream volume, there has been a steady increase in the per-capita milk consumption in the city in spite of the increasing costs of sanitary measures. Conversely milk consumption in our southern cities is for the most part at a rate which dietitians believe to be below the necessary minimum for proper nutrition. The chief difference between these two situations is one of temperature and the attendant ease or difficulty of preservation. This observation applies quite as fully to meat and to many other perishable food products. It is all the more necessary, therefore, both as a matter of sanitation, of nutrition and of economics, that attention should be given to the preservation of perishable foods. Perishability is nature's off-set to that tremendous climatic advantage which the south enjoys, and which so greatly favors cheap food production. Food preservation may take any one of many forms, chief among which we may mention dehydration, pickling, either by means of brine or by means of concentrated syrups, smoking, canning, in which complete sterilization by heat is the means of preservation, and cold storage.

Partial dehydration of fruits is, of course, well known in all parts of

the world. The more complete dehydration of various vegetable products, fruit juices, eggs and whole milk that is now commercially feasible are perhaps less well known, but represent promising economical methods of preservation. Pickling, smoking, and canning call for little comment. Cold storage is probably our most valuable means of preservation, since it least alters the physical and chemical properties of the food, and does not ordinarily modify its appearance. All of these processes have their sanitary problems, but these are not unique and merely have to do with such ordinary rules of cleanliness as would be observed in any fresh food supply.

It is unfortunately the case that the food preservation industries have suffered in the past from gross abuses, the basis of which has been the attempt to preserve food-stuffs which were otherwise unmarketable by reason of their condition of decomposition or general dirtiness. This is not, however, a necessary feature of food preservation, and should be controlled, as all other food handling is controlled, without prejudice to the processes themselves which are of the utmost value.

On the occasion of a recent visit to Porto Rico, I was surprised to find to what a large extent the inhabitants of that densely populated island are dependent upon desiccated, canned and preserved foods. With their abundant agricultural resources devoted almost wholly to sugar, tobacco, coffee and fruit, their laborers live upon rice and beans, and canned goods. In the opinions of those most competent to judge, malnutrition is a basic and fundamental cause of a very large proportion of the annual death rate. Here we have an excellent opportunity to study an experimental condition, ready made, relating to an optimum dietary which is limited to desiccated and preserved foods. I am happy to say that such a study is well under way at the School of Tropical Medicine of Columbia University and the University of Porto Rico.

CLOTHING

Clothing is variously used for protection of the body, for adornment and in compliance with the normal dictates of modesty. The extent to which, under various conditions, one or another of these functions is made the dominant one at the expense of the others makes an interesting study in human nature.

Thus far we lack any adequate scientific study of the protective value of clothing. We do know that the effects of a wide range of climatic conditions can be reduced and brought within the comparatively narrow range of the body's own adaptability by suitable clothing. In the more refined terms of our ventilation studies, where the elimination of body heat is the controlling factor, the relationship between clothing and optimum air conditions is an intimate one. Beyond this general statement we cannot venture at the present time.

LIGHTING

In our discussion of atmospheric pollution we have touched briefly upon the physiological effects of sunlight. Much more of interest could be said in this connection and also in connection with the therapeutic uses of certain artificial lights, especialy ultraviolet light. Many of these matters are certain to attract more of our attention in the near future.

For the present, however, we pass rapidly over this interesting field to a consideration of the relation of light to vision. The human eye probably exhibits a wider range of adaptability than any other physiological mechanism which we have thus far considered. Professor Janet Howell Clarke states that the limits of the range of retinal sensibility to light are in the ratio of ten million to one. It becomes a matter of very practical interest, therefore, to determine if there be an optimum point on this extensive scale of lighting intensity. Here again, as in the case of standards for air conditions, we find that other factors such as specific conditions of use, age and occupation, and also such matters as contrast and departure from the average of illumination have to be considered. With the eye adjusted to daylight conditions, illumination intensities that would be quite sufficient at night are found to be too low for effective results. Here again, I believe, that the theorem of the mid-point between the limits of adaptation may be applied to determine an approximate optimum. In this case, however, the most comfortable degree of illumination for normal seeing under average conditions of employment is found at an intensity somewhere near the mean value of the iris opening. On the other hand, we are learning that for the maximum efficiency in occupations which depend largely upon the visual function, such, for example, as

inspecting small machine parts, illumination intensities considerably in excess of those required for maximum comfort under normal conditions of use are indicated. The tendency is in the direction of greater intensities of illumination in general. Whether this indicates that we are approximating more nearly a true optimum condition, or whether it indicates that we are merely speeding up at the expense of the useful life of the machine remains to be determined by the experience of the future. Certain it is that the ever diminishing cost of artificial illumination has made it possible for us to consider this entire subject upon its merits and provide for any particular situation, that degree and kind of lighting which, in the long run, shall prove most beneficial.

A phase of this matter which has not hitherto received serious consideration is that of the quality of light as distinguished from its quantity. The so-called white light of out-of-doors is a spectral mixture of somewhat indefinite and variable composition. It represents, however, the quality of light to which the human eye has become adjusted. It is a matter well worthy of further study as to whether some of the defects of artificial illumination are not due to departures from the spectral composition of white light rather than to lack of intensity.

INSECT CONTROL

One might set down, as a feature of the environment worthy of study, competitive life in all forms from the bacteria to the beasts of the jungle. We have, in fact, dealt with the former, in association with water and food and we of today know little of danger from wild beasts. The class *Insecta*, however, as represented by several of its orders, furnishes a new type of menace. Various species of insects may carry infection to man, either by purely mechanical means, or by serving as a secondary host in the life cycle of an organism pathogenic to man. The fly, the mosquito and the louse, come to our minds at once in this connection as conveyors of typhoid fever and other intestinal infections; malaria and yellow fever; and typhus fever respectively. The flea also, in association with the rat, is the carrier of bubonic plague.

In all cases our most effective control of insect pests is by eradication, and, in general, the most vulnerable point of attack is the breed-

ing ground. But it is only necessary to break the chain at one point and at least two other points of attack are open.

If the malaria or yellow fever patient be screened from mosquitoes, transmission of the disease cannot occur. Similarly much protection is had by preventing access of flies to typhoid excreta. Furthermore, infected insects must reach a victim, directly in the case of the mosquito, indirectly in the case of the fly, and here again screening is effective.

The war upon the rat and associated flea is of similar nature. We attempt to eradicate by the elimination of breeding grounds, we "screen" against infection of the rat colony by ship quarantine and disinfection, and we rat proof the homes to prevent contact.

SOME PRESENT DAY PROBLEMS

I cannot close this cursory and possibly somewhat sketchy review of the environment, as related to public health, without outlining some of the outstanding problems of the present day. It has become rather customary of late years for those engaged in public health activities to write graceful epitaphs about the Sanitary Engineer. To one familiar with the present and future problems in the control of the environment, the special field of the engineer, these announcements recall the predicament with regard to his demise from which Mark Twain so cleverly extricated himself. In truth the sanitary engineer of yesterday, who worked so successfully in the fields of water supply and sewerage, has broadened into the public health engineer of today, working in the whole field of environmental control. His fundamental data are necessarily the facts of the biological sciences, especially of bacteriology, zoology and physiology; his methods, those of physics and engineering. His educational training must be such as to cause him to view all his tasks against a public health, rather than a strictly engineering background. His objectives are the preservation of the public health.

To men of such qualifications, working in close contact and entire harmony with their associates in the biological and medical fields the opportunity for service is greater than ever before.

In the field of heating and ventilation, we are still far from any final solution of the optimum condition, expressed in general terms. The

relation of radiant heat, a dominant factor in any attempted solution, is still an unknown and neglected item. We have no single instrumental measure of the various qualities of air which enter into the composite item of comfort. Perhaps we do not even know all those qualities. My personal feeling is that there are at least two, as yet undefined qualities that are hidden in the so-called "freshness" character of air. The relation of clothing to the process of heat elimination from the body has yet to be considered.

We have advanced far in water purification practice and in the art of sewage disposal. The next two decades are bound to develop the practice of sewage disposal. Stream cleaning and protection are the next big items in our sanitary program, for the margin between increasing stream pollution and the safe loading of water purification plants is already becoming dangerously small in many important water sheds.

Where there is much controversy there is always need for further study and that is the present situation in regard to pasteurization of milk. The whole subject has just grown like Topsy and must be thoroughly overhauled and reconstructed on sound engineering principles before we shall ever be satisfied with the result. Fortunately that work is now well under way.

We are just getting interested in lighting, and an immense field of research and practical application is there before us. Here again rapidly changing opinion and many opposing views as to standards indicate a growing subject, and the need of investigation.

In rural sanitation, in drainage and mosquito control, in the economical collection and disposal of municipal refuse and in various other lines of environmental control the public health engineer still has an abundant opportunity for the exercise of his best talents. If his work does not result in such spectacular reductions in the death rates as followed water purification, for example, it will at least leave its unmistakable mark upon our communities as, little by little, controlling the environment and adapting it to human needs and comfort, he eases the strain upon the powers of human adaptation, by meeting that marvelous adaptation of internal to external relations, by an equally important adjustment of the environment to physiological requirements.

SOME CRITERIA OF THE RESULTS OF MALARIA CONTROL MEASURES

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By control measures we mean anything which will so far interfere with the development cycle of the malaria parasite as to materially affect the incidence of the disease in a population. This cycle may be briefly reviewed: The gametocytes, or sexual forms of the parasite, are produced in man; fertilization takes place in the anopheline mosquito and sporozoites are produced there; through the bite of the mosquito these sporozoites are transferred to the blood of man, where, after a varying number of asexual generations, the sexual forms of the parasite are produced.

The parasite requires two hosts, then, and one of them, the insect, must find favorable aquatic as well as terrestrial conditions for its development. Thus, the transmission of the disease depends on many different factors and the parasite is vulnerable at several points. The mosquitoes may be attacked in their aquatic stage by the elimination of their breeding places or by the use of larvicides or of natural enemies of larvae. Adult mosquitoes may be destroyed in or about human dwellings. Access of the mosquito to man may be hindered by bed nets or house screens, by the use of chemical repellants, or, possibly by the employment of domestic animals which may divert the female mosquito in its search for blood. In the human host quinine or other drugs may be employed to prevent infection or to cure the disease before gametocytes can be formed. The living conditions of man may be so improved that he becomes less liable to relapse and more amenable to cure.

Control measures, then, are many; and there is scarcely one of those I have mentioned which has not been employed at some time.

The results of our control measures may be estimated by the gross amount of malaria in the region under treatment before and after con-

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trol work is attempted. Or, we may measure the effect of the particular agent employed. If, for example, larva-destroying fish are introduced into a region, our criterion of results would be the number of Anopheles produced before and after the colonization of the fish.

We will consider severally the means commonly employed for measuring the amount of malaria in a population and the limitations of each method.

The blood parasite rate, as the term is commonly employed, means the proportion of a population found to be harboring malaria parasites, as determined by the examination of stained blood films taken from a representative sample of the people. Generally the parasite rate is based on a single examination, but in smaller populations sometimes more than one film is taken of each person, or the examination is repeated. Usually the sample of the population examined is made to include a considerable number of that class of persons most likely to harbor parasites, as children of school age. If the parasite rate among the sick is taken, it is recorded separately.

The limitations in the value of the blood parasite rate are obvious. Only those persons will be found positive who harbor sufficient parasites to be discoverable by microscopic means in a single drop of peripheral blood. In many infected cases parasites occur only in the internal organs, or are too few in the peripheral blood for detection. No reliable serological test is known, and a large proportion of persons actually carrying parasites will be missed.

The work has to be done by a trained and conscientious microscopist, and if a large population has to be done the labor is not small. The use of the thick film will greatly lighten the task and add to the reliability of the results. I have had now some thirteen years' experience with the thick film method, and I can vouch for its usefulness in malaria surveys. I believe that most useful results can be obtained by a short examination of each thick film. A large number can be done by the same skilled examiner; the error due to the personal equation and to random sampling is thereby diminished, and a sufficiently large proportion of the infected persons obtained to afford a useful standard of comparison. The time that one should give to each thick film before declaring it negative depends on the experience of the examiner, who must determine for himself the amount of error due to shortening the time devoted to specimens apparently negative.

Besides affording a most useful standard of comparison of the malaria rate, the examination of the blood gives us valuable knowledge of the different species of parasites present, the stages in which they occur, and the numbers per individual. Some writers question the possibility of distinguishing between tertian and quartan in the thick film. I have recently had a large experience in the examination of a group where quartan was abundant. In but few cases was it difficult to distinguish between the two types.

The spleen rate, in the words of Christophers (1), is the percentage of persons with enlarged spleen in any given community. It is commonly determined by palpation and has the great advantage of convenience. Comparatively little time is required for the examination of a large sample of a population, and the same skilled examiner can do all of a large series. The error due to the personal equation is thus diminished and results useful for comparison are obtained. The spleen rate of children 2 to 10 years of age is often taken as representative of the endemic malaria rate of a population, and children in schools offer a convenient sample.

The spleen rate measures one of the clinical effects of malaria infection. The degree of enlargement of the spleen should then be noted. The "average spleen" of Ross (2) "is a weighted average in which normal spleens are valued at 1, other spleens at figures representing the relative volume of the different sized spleens noted." Several different methods are in use for recording the size of the spleen as palpated, the details of which need not be considered here. The shape and consistency of the enlarged spleen, its relation to certain more or less fixed points, as the costal margin and the umbilicus, and its relation to the size and age of the patient are usually taken into consideration.

The significance of spleens palpable only on deep inspiration is of much importance in malaria surveys among children. Apparently such spleens may be found among normal children.

Zamkin (6) examined 2,100 apparently normal children in New York City to determine the variation in the size of the spleen and liver. He found 25 per cent of spleens palpable below the free border of the ribs. The frequency of the splenomegaly was greatest during the first year of age. In children of five to nine years of age, however,

he found 25 per cent with spleens palpable, and in children of ten to twelve years, 10.6 per cent. It is to be noted that these two age groups include children commonly examined in malaria surveys.

Again, splenomegaly may be caused by diseases other than malaria. In some countries enlargement due to kala-azar must be considered, but Price and Strickland (3) conclude that when the clinical signs of kala-azar are not well marked, the splenomegaly of a community living in kala-azar infected area is due to malaria.

At all events, the error due to kala-azar is limited to certain regions. Some more common causes of splenomegaly have to be considered: Fort (4) states that measles may be a cause of splenomegaly. In a group of children examined by him 85 per cent had spleens palpable thirty days after a measles epidemic. After six months, 20 per cent were still palpable. In 20 cases examined, a spleen enlargement followed an attack of tonsillitis. Bleyer (5) noted a well-marked enlargement of the spleen of children during measles rash and for several days following it. During the two weeks following the disappearance of the rash, the spleen was palpated at or below the costal margin in about 15 per cent of cases. There seemed to be no connection between the severity of the cases and the degree of splenomegaly.

Dr. K. F. Maxcy and I have recently done some work to determine the significance in malariometry of the spleen, palpable only on deep inspiration among children. We compared groups of school children in the Delta region of the Mississippi Valley with those in two non-malarious regions. Our results will soon be published and need not be elaborated here, but it appeared plainly that a large proportion of the spleens, palpable only on deep inspiration, were normal, or, where pathological, were due to causes other than malaria.

The examination of groups of children in regions known to be non-malarious affords a most useful standard of comparison. A classical illustration of such examination is that of Ross, Christophers and Perry (7) who examined 469 normal London school children and found only 1.07 per cent with palpable spleen. Their results should not be taken as representative of every non-malarious region or of every method of examination. Further examinations of children in various non-malarious regions should be made, and these examinations done at different times of the year. Certainly, the malariologist who intends

to make a large use of the spleen rate should first establish his standard by the examination of considerable numbers of children in regions known to be non-malarious.

Whatever the significance of spleens palpable only on deep inspiration, the proportion of spleens enlarged to or below the costal margin is of unquestioned significance in malariometry. Malaria is one of the chief causes of splenomegaly. Malaria workers, especially in the tropics, have for many years made a large use of this method of estimating malaria and they universally consider it trustworthy. Further research regarding the character of the normal spleen and of the causes of splenomegaly other than malaria, may eliminate some of the errors in the use of this index and give it a higher value in both tropical and temperate climates. Certainly the gross sources of error should be considered before we go too far into detailed methods of measurement and complex mathematical formulae for expressing results.

The hemoglobin index and the amount of secondary anemia are sometimes included in a malaria survey. Their value, as indices of the gross amount of malaria, is limited, of course, by the fact that other diseases, notably hookworm disease, may be co-extensive with malaria and produce similar effects on the blood; but these indices may be profitably employed in the comparison of endemic and epidemic malaria or other measurement of the effects on a population of malaria infection.

A complete survey of a population should include more than the gross parasite, spleen or hemoglobin indices. One should consider the relation of each rate to the other and the relation of all to race, age, amount of treatment and the physical condition of the population, as well as their relation to the periods of greatest transmission of malaria. The significance of some of these relationships may be illustrated by certain examples:

A high estivo-autumnal index is often associated with periods of great anopheline intensity and the rapid transmission of malaria. High tertian or quartan rates are often found in regions where the period of malaria transmission is long interrupted by cold or dry seasons. This relationship is not universal. Benign tertian epidemics may occur during the mosquito season in the tropics although estivo-autumnal carriers may be present, and estivo-autumnal may predomi-

nate during and after long periods of latency of infection. I recently assisted in the examination of about 7,000 West Indian laborers, the great proportion of whom were apparently well and able-bodied. The malaria parasite rate was high, nearly 29 per cent, and the type of parasite nearly three-fourths estivo-autumnal and one-fourth quartan. The proportion of tertian was negligible.

Spleen enlargement may appear in the population late after an epidemic, and reach its maximum rate long after the maximum parasite rate has past. Spleen, parasite and hemoglobin rates vary with the periods of greatest transmission. The incidence of these rates in age groups is of significance. In regions of high endemic malaria children usually show the higher spleen and parasite rates. Adults, through acquired immunity or survival of the most resistant, may show relatively low rates. A notable example of this relation is shown by negroes in certain parts of Africa. But where a population ordinarily exempt is subjected to a malaria epidemic, the spleen and parasite rates may show a different age distribution. The classes most exposed to infection may exhibit the higher rates.

Enough has been said to illustrate how the various indices used in malariometry may vary with circumstances, and how great a variety of deductions can be made from the findings. The interpretation and value of different criteria vary greatly with the character of the population examined; a generalization valid in one locality may not hold good in another.

History rates have often been the sole criterion employed of the success of malaria control measures. They offer a most uncertain standard unless carefully obtained and recorded. Malaria is a disease which varies greatly in its manifestations, and is often made a scapegoat for doubtful diagnosis in the patient. In the diagnosis of a population, especially where control measures are being employed, the history rate is subject to additional errors. Physicians are usually sympathetic to health-improvement programs, and their judgment may be more influenced by the thing hoped for than by the thing that is.

Different physicians may give greatly varying opinions as to the amount of malaria in a community; one group stating that it is plentiful, another, denying its existence there. History rates are especially uncertain in regions where, owing to natural causes, malaria has

greatly diminished; the tradition outlasts the disease. Histories offer valuable guides in malaria work, but unless supported by blood examinations or other objective evidence, they rarely furnish reliable criteria.

The symptomatology of malaria, often indefinite in character, is sometimes unmistakable. We can often obtain valuable information from histories by ascertaining roughly the proportion of cases which showed a marked tertian type of fever associated with other more definite characteristics. In the study of past epidemics we can occasionally get worth while evidence in this way.

The results of the individual measures used in malaria control are estimated in various ways. The immediate effect of a larvicide or of fish control may be ascertained by an inspection of the breeding places of the mosquitoes. That extremely doubtful measure, the use of bats to destroy adult Anopheles, may be tested by the examination, often disappointing, of the stomach contents of the animals. For all mosquito-destroying agents the final criterion, of course, is a census of adult mosquitoes taken before and after the measures are put into effect.

In going over the results of malaria control campaigns we sometimes find the statement that Anopheles were reduced, but we can find no adequate measure of the amount of reduction. Yet the reduction in the numbers of Anopheles in the most valuable criterion we have of the efficacy of a mosquito-destroying measure, whether larvicides, natural enemies, drainage, clearing of streams or other means. The incidence of adult Anopheles in a region may often be measured by the numbers found in preferred day-time resting places, such as dwellings, barns or other outhouses, hollow trees, culverts and the like. It is important to note not only the numbers, but also the species of Anopheles found, the relation of resting to breeding places, and the proportion of individuals engorged with blood.

Generally speaking, Anopheles more than other species of mosquitoes tend to congregate in these shelters. Different species, however, vary greatly in their choice of day-time resting places. *Anopheles quadrimaculatus*, the commonest malaria carrier in the southern United States, has a marked tendency to remain in dwellings, outhouses and shelters relatively accessible to the census-taker.

Other species, notably some of the chief malaria carriers of Central America, prefer the jungle and congregate in houses only when the total mosquito intensity is great. In any species the numbers found resting in dwellings can only partially reveal the numbers which may have entered during the night, bitten, and flown away to other shelters. Various devices have been used to entrap the more elusive species. Bed nets, ragged or improperly adjusted, often contain the mosquitoes when none can be found elsewhere in the room. Specially devised window traps have proved useful. Domestic animals or human beings are placed in exposed places and kept under observation for long periods during the night and mosquitoes are caught in the act of biting them. Or large traps may be baited with man or domestic animals and the engorged mosquitoes collected at dawn.

It is of especial importance to maintain census stations in a neighboring untreated locality in order to obtain a reliable control of the variation in anopheline intensity due to causes other than our anti-mosquito measures. Periods of drought may effect remarkable reductions in the mosquito population. I remember one locality where there was a most gratifying reduction in Anopheles following the use of larvicides, but the mosquitoes in a similar locality unaffected by the larvicides showed a similar reduction. Only the use of proper controls can tell us how much credit to give our own efforts and how much is due to the weather.

I can appreciate from my own experience the difficulties which are met with in many regions, especially certain tropical ones, in obtaining even an approximate anopheline intensity index. Often only the greatest ingenuity and persistence will avail anything. Unhappily we have not yet devised a chemical attractant which would assemble Anopheles for a census as carrion does vultures.

The efficacy of screens, bed-nets and repellants may also be subjected to immediate tests. It is not enough to rely on malaria rates before and after their use as a measure of their efficiency. One should know what proportion of the mosquitoes are kept out of screened dwellings, whether they are coming down the chimneys or entering through doors or windows carelessly left open. The comparison of the numbers of Anopheles found in screened and unscreened dwellings is an essential criterion of the success of the measure. The efficiency of bed

nets can often be determined by the numbers of Anopheles found in them, especially if one examines them early enough in the morning. The habits of the people with reference to the use of screens is important. Any screening measure, however perfect mechanically, will fail if the occupants of the dwelling spend their evenings on an unprotected veranda. Possibly no measure depends so much on the education and intelligence of the users as screening.

In estimating the result of quinine treatment or any control measure applied directly to man, we are in general limited to the same means as those employed for measuring the gross malaria rate, except that we may deal with smaller groups and control groups are more easily available. The number of clinical attacks or the number of days lost from work may enter into the reckoning.

The proportion of Anopheles found infected in nature has often been used to determine the susceptibility to malaria and the blood-feeding habits of the different species of Anopheles found in a locality. This test also roughly measures the number of gametocyte carriers found in the human population; and it has been proposed that the infection rate of wild mosquitoes may be used as a measure of the result of the use of quinine or other treatment on the incidence of gametocyte carriers. The proportion of such infected mosquitoes is usually so small, however, and is so much influenced by season, abundance of Anopheles and degree of exposure to their bites, that only a very large series of mosquito dissections would give results at all reliable. In a region where the malaria rate is very high, such method of measurement would be worth trying.

Uhlenhuth (8) in Germany used the precipitin test to determine the origin of the blood found in the stomachs of Anopheles, a method that has been developed in this country by Bull and King (9) and used by them in comparing the blood preferences of different species of Anopheles. They (10) have used this method in a study of the efficacy of the partial screening of dwellings. The number of Anopheles found in such houses was relatively small, but the proportion of them containing human blood was larger than among those found in unscreened houses—a result which offered some explanation of the observed inefficacy of partial screening in a certain region of Louisiana. This criterion is especially useful in judging the results of the introduction of domestic animals as a control measure.

The limitation of all these tests seems to lie in the fact that mosquitoes are by no means constant in their feeding habits. Only long series carried out under different conditions can give us reliable criteria.

Many malaria control campaigns have been conducted in various parts of the world during the past twenty-five or thirty years. In this country alone some 100 have been done since 1922. The results of these campaigns have usually been measured by the diminution in the gross malaria rate; the effect of the particular means employed has often been inadequately measured. In some campaigns, especially those done in recent years, both the gross results and the results of the particular measures have received careful attention. Generally, however, the records of control measures have left us in doubt as to how much was due to conscious efforts, or, if several measures were employed, how much weight to ascribe to each. We are not always sure whether to praise quinine or the ditch.

I do not wish to seem to belittle the results of this malaria work. I believe that a study of the abundant literature of these campaigns will convince one that a large number of them, the majority, perhaps, brought about a material reduction in malaria. In some, of course, we have to make allowances for the enthusiastic and sometimes partial judgment of the worker, his zeal for propaganda and his failure to appreciate the normal fluctuations in the malaria rate; but, all things considered, there remains a large residuum of solid results. Not only have such efforts brought about a reduction of insect-borne disease, but they have also furnished some useful by-products. Land has been reclaimed, roads improved, unsightly bodies of water and pest mosquitoes abolished and the installation of sewers and of other health work stimulated. Even imaginary malaria may serve as a lever to raise a backward community to a higher esthetic and hygienic plane.

Furthermore, many of these malaria campaigns were primarily emergency measures. An epidemic may have made it necessary to do something at once. It was not always possible to adequately measure the malaria incidence or other conditions present even of the year when the work was begun. Financial considerations had to be met. A community sometimes votes funds for the work late in the season, funds which have to be used at once, if at all.

Much has been learned and unlearned in this work, but the great bulk of experience has left us lacking in knowledge of many phases of malaria control. Our need of more precise knowledge may be illustrated by the wide differences fo opinion which prevail regarding the value of the most fundamental measures. One might even speak of schools of methods of malaria control, some of them more or less national in character. Schools of protection by domestic animals, of major drainage, of quinine treatment, of hygienic betterment of the population, and the like.

In this connection I will quote a statement made by James (11):

> I do not hesitate to affirm that in nature the only mosquitoes which succeed in transmitting malaria are those rare individuals who happen to pass their life in conditions which resemble very closely those which we have found to be essential for the successful transmission of disease in experimental work. No one who fully appreciates the importance of this conclusion and accepts it as true can fail to regard anti-mosquito measures for dealing with malaria from a new point of view. He will at least realize what a great waste of effort is involved in measures directed against the breeding places of mosquitoes as a whole, and even in similar measures directed against one species. He will begin to appreciate how the secret of a successful control of malaria lies not in the general knowledge that the disease is spread by mosquitoes of a certain kind, but in the particular and exact knowledge of the life history of the few individual mosquitoes which succeed in becoming transmitters of the disease.

One would infer from this statement that control measures should be directed against adult mosquitoes, especially those found in dwellings, rather than against mosquito larvae. The validity of much of the past work in malaria control is challenged. It will be remembered that the laboratory work of Colonel James was done with *Plasmodium vivax* and *Anopheles maculipennis* in England, and he states (12) that he would not extend his conclusions to control measures outside of Europe. Certainly, in some parts of the United States and of tropical countries, with which I am familiar, malaria parasites do not so far depend on the most favored mosquitoes for their existence as does *Plasmodium vivax* in northern Europe, and the outlook of measures directed against the breeding places of mosquitoes is not so pessimistic. The fact, however, that Colonel James should thus far question the validity of anti-larval measures anywhere would indicate that

he does not believe that such method of control now stands on a very secure scientific basis.

I will mention certain particular problems which need further research:

1. The participation of different species of Anopheles in the transmission of malaria. To what extent is transmission due to specific differences in susceptibility and to what extent to mosquito habits and local conditions. Considerable evidence has been adduced to show that a species harmless in one locality may be an important carrier in another one.

2. The relation of anopheline intensity to transmission of malaria. Probably here we deal with a sliding scale. The more intense the malaria rate the fewer the anophelines required to keep it up.

3. The possibility of limiting anti-mosquito measures to certain seasons of greatest transmission. In the southern United States intensive measures might be limited to late summer and early autumn.

4. Distance of effective flight of Anopheles. This distance is usually put at about two kilometers, but it has not been precisely determined for all species and all localities.

5. The value of quinine prophylaxis and of the quinine treatment of populations, and of the efficacy of plasmochin or other drugs.

6. The value of killing mosquitoes in dwellings, or of mosquito traps.

7. The significance of spleen and blood parasite indices and the best methods of their measurement.

I mention these problems merely as illustrations of our lack of precise knowledge and of the need for further research. The malariologist should be in a position to advise more definitely on the best methods of control, given a particular set of conditions. It may be well to consider briefly some possible means of increasing our knowledge.

The standardization of methods of carrying out control measures and of recording their results has been proposed. This plan has much in its favor. The act of formulating standards would have the stimulating effect of making us take stock of our knowledge. Such standards would of necessity have to be made very elastic in order to meet varying conditions, but the worker could choose such as would best suit his particular problem; the list would serve as a useful memo-

randum at least. The chief difficulties would be met in the attempt to standardize methods in which there is no general agreement among malariologists. At the Fourth Congress of the Far Eastern Association of Tropical Medicine in 1921 a committee was appointed to report on the best method of measuring and recording the size of the enlarged spleen. It was unable to recommend any existing method as entirely satisfactory and pointed out the desirability of further investigation in the matter [vid. Christophers (13)]. In no case should the worker allow himself to attempt more tests than he can carry out thoroughly and accurately. In our ambition to learn the whole truth we should be sure that we get nothing but the truth. The minimum requirement should certainly include sufficient measurements to determine whether a possible reduction is due to control measures or to normal fluctuations in the malaria rate. Epidemics come and go, seasons and populations vary, and in some regions there is a steady decline of malaria due to unknown factors. The measurement of the gross rate of malaria should, theoretically, extend over some years before control measures are put into effect, an ideal which is rarely possible to attain.

In some cases it is possible to choose localities for control work which offer conditions little complicated and especially favorable for experiment. In some highly malarious regions the breeding places of Anopheles are limited. Sea, mountains, or desert may aid in delimiting the problem. The less migratory the human and the mosquito populations the better for research, and the higher the malaria prevalence in a community the better our opportunities for obtaining a measurable result. Comparison of results in these more favorable localities with those obtained in more complex regions may aid in bracketing our problems.

Even in regions possessing no special physical features malaria is often so localized that we can restrict our field of research, provided there is not too much shifting of the population. We can often learn much by the study of conditions as they exist. I believe that one of the most fruitful fields of malaria investigation lies in the comparison of malaria incidence in different localities in which no control measures have been practiced.

In many cases, however, control measures are demanded and we cannot pick and choose our ground. We must make the best of con-

ditions as we find them. Where we cannot even measure adequately the amount of malaria present at the beginning of control we may still obtain valuable data by measuring as accurately as possible the effects of the particular measure employed—the reduction in mosquito intensity, the sterilization of particular breeding places, the reduction in the sick rate, and the like—always seeking for suitable controls. Careful records of particular results may contribute to the final solution of some of the problems. We must learn as we work; it is a poor field which yields no grain.

Years of carefully controlled work may be required to establish our knowledge of malaria control measures on a firm basis. We trust, however, that we will profit more rapidly by experience in the treatment of populations by control measures than we have in the treatment of the individual by quinine. This remedy has been used by noble and peasant, priest and laity, by the learned and unlearned for over 250 years, yet to-day there is no substantial agreement as to proper dosage or even as to the fundamental question as to what extent the remedy acts directly on the patient or indirectly by increasing his power of resistance to the disease. It is to be hoped that an experience of less than two and a half centuries will suffice to put our methods of malaria prevention on a firmer basis than that on which malaria cure at present rests.

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